

European Heart Journal (2001) 22, 2125–2130
doi:10.1053/euhj.2001.2892, available online at <http://www.idealibrary.com> on **IDEAL**[®]

Coronary restenosis elimination with a sirolimus eluting stent

First European human experience with 6-month angiographic and intravascular ultrasonic follow-up

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Aims Coronary stenting is limited by a 10%–60% restenosis rate due to neointimal hyperplasia. Sirolimus is a macrocyclic lactone agent that interacts with cell-cycle regulating proteins and inhibits cell division between phases G1 and S1. The hypothesis tested in this study is that local delivery of sirolimus with an eluting stent can prevent restenosis.

Methods and Results Fifteen patients were treated with 18 mm sirolimus eluting BX VELOCITY[®] stents. Quantitative angiography and three-dimensional quantitative intravascular ultrasound were performed at implantation and at the 6 months follow-up. All stent implantations were successful. One patient died on day 2, of cerebral haemorrhage and one patient suffered a subacute stent occlusion due to edge dissection (re-PTCA, CKMB 42). At 9 months no further adverse events had occurred and all patients were angina free. Quantitative coronary angiography revealed no change in minimal lumen diameter and

percent diameter stenosis and hence no in-lesion or in-stent restenosis. Quantitative intravascular ultrasound showed that intimal hyperplasia volume and percent obstruction volume at follow-up were negligible at 5.3 mm³ and 1.8%, respectively. No edge effect was observed in the segments proximal and distal to the stents.

Conclusion Implantation of a sirolimus-eluting stent seems to effectively prevent intimal hyperplasia. (*Eur Heart J* 2001; 22: 2125–2130, doi:10.1053/euhj.2001.2892)

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Key Words: Coronary artery disease, PTCA, stenting, restenosis prevention, sirolimus, eluting stent.

See page 2054 for the Editorial comment on this article

Introduction

Restenosis is the most important limitation of the long-term success of percutaneous coronary interventions. Depending on lesion and patient factors, restenosis occurs in 10%–60% of patients treated^[1].

Restenosis not only has an economic impact but it also restricts application of percutaneous coronary angiography to short lesions in larger vessels and to coronary artery disease that is not too extensive. Restenosis following balloon angioplasty has been shown to

result from three processes; early elastic recoil, negative arterial remodelling and neointimal hyperplasia^[2]. Intracoronary stenting effectively prevents recoil and negative remodelling so that in-stent restenosis is caused almost exclusively by intimal hyperplasia^[3]. The proliferation of vascular smooth muscle cells and extracellular matrix synthesis, triggered by the balloon or stent trauma, progressively encroaches upon the arterial lumen. Pharmacological strategies to reduce intimal hyperplasia have been tried with a myriad of drugs, but almost all failed in humans^[1]. One possible reason for this failure is that systemically administered drugs cannot reach sufficient concentrations locally to prevent the intimal hyperplastic reaction. There has been some limited success with local drug delivery using special delivery balloons^[4]. But the low efficiency of drug delivery and low retention of the pharmacological agents limit the efficacy of this technique. Another platform for

Revision submitted 13 July 2001, and accepted 18 July 2001.

This study was sponsored by Cordis Corporation, Warren, NJ, U.S.A.

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0195-668X/01/222125+06 \$35.00/0

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CORD109138
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Table 1 Baseline characteristics

n=15	
Male	10
Age (years)	60 (35–80)
Stable angina	6
Unstable angina	9
Braunwald IB	2
Braunwald IIB	5
Braunwald IIIB	2
1 vessel disease	13
2 vessel disease	2
Treated vessel	
LAD	6
LCX	5
RCA	4
Time to follow-up angiogram (days)	190 (112–217)

Table 3 Three-dimensional quantitative intravascular ultrasound

3D QIVUS at 6 months follow-up angiography	
Lumen volume (mm ³)	154.3 ± 60.9
Stent volume (mm ³)	161.2 ± 73
Neointimal hyperplasia (mm ³)	5.3 ± 17.0
% obstruction volume	1.8 ± 4.8

QIVUS=quantitative intravascular ultrasound.

local drug delivery is a coronary stent with a drug eluting coating. Using the stent as a delivery device has the further advantage of allowing drug administration over an extended period of time.

Local administration of drugs that inhibit vascular smooth muscle cell proliferation is thus potentially a very attractive means for prevention of in-stent restenosis. Sirolimus (rapamycin) is a macrocyclic lactone that inhibits cell division between G1 to S phases. It has been shown to effectively inhibit intimal hyperplasia after balloon and stent injury in animals^{15–21}. The drug

eluting stent used in this study delivers sirolimus locally for several weeks at high concentrations without the risk of adverse systemic events.

Recently Sousa *et al.*¹⁰ reported the 4 month clinical and angiographic results with a sirolimus eluting BX VELOCITY[®] stent implanted in 30 patients with single vessel de-novo coronary artery disease. Surprisingly an almost complete absence of neointimal hyperplasia was seen at the 4 month follow-up.

In the present safety and feasibility study we sought to determine the effects of a sirolimus-eluting BX VELOCITY[®] stent at 6 months, not only clinically but also by quantitative coronary angiography and quantitative three-dimensional intravascular ultrasound.

Both patient cohorts are part of the pioneering First In Man (FIM) sirolimus eluting stent safety and feasibility study. The 30 patients in Brazil were treated with either a slow eluting formulation (n=15) or a fast eluting formulation (n=15) of the sirolimus stent. The 15 Rotterdam patients were treated with the slow eluting stent.

Methods

Both stable and unstable patients with symptomatic or functionally significant single vessel, de-novo, coronary artery disease were included in the study. Lesion length had to be <15 mm and vessel diameter ≥3.0 mm by visual assessment. Depressed left ventricular function (EF ≤30%), total occlusions, main stem stenosis and lesions involving side branches <2 mm were angiographic exclusion criteria. Patients were treated with single, 18 mm long, sirolimus eluting, balloon expandable, over the wire, BX VELOCITY[®] stents (Cordis co, Warren NJ). The stent coating consisted of a fixed amount of sirolimus (140 µg per cm² metal surface area for a total of 150–180 µg of sirolimus/stent) blended with a mixture of non-erodable polymers. A sealing layer was applied to the coating to ensure release of drug

Table 2 Quantitative coronary angiography, 13 patients with follow-up angiogram

	Vessel segment	In stent
Reference diameter pre (mm)	2.73 (2.25–3.33)	
MLD pre (mm)	1.00 (0.58–1.58)	
Diameter stenosis pre (%)	63.5 (53–76)	
Lesion length (mm)	9.31 (4.85–13.93)	
Reference diameter post (mm)	2.79 (2.29–3.26)	
MLD post (mm)	2.11 (1.70–2.80)	2.54 (2.05–3.05)
Diameter stenosis post (%)	24.4 (11.5–38.0)	12.0 (3.0–19.0)
Reference diameter follow-up (mm)	2.76 (1.76–3.43)	
MLD follow-up (mm)	2.09 (1.50–2.77)	2.54 (2.1–3.04)
Diameter stenosis follow-up (%)	25.3 (9.0–41.5)	13.7 (6.5–24)
Loss in MLD (mm)	0.02 (–0.47–0.46)	0.00 (–0.37–0.25)

Results expressed as means with range. MLD=minimal lumen diameter; pre=before procedure; post=after stent implantation.

Table 4 Quantitative coronary ultrasound

	Proximal segment	P	Stent	P	Distal segment	P
Mean lumen area post (mm ²)	7.7 ± 3.4	0.9	7.0 ± 1.6	0.99	7.1 ± 3.0	0.73
Mean lumen area follow-up (mm ²)	7.7 ± 4.3		6.9 ± 1.8		7.0 ± 3.3	
Mean vessel area post (mm ²)	14.5 ± 5.0	ns			11.5 ± 4.6	ns
Mean vessel area follow-up (mm ²)	14.0 ± 4.4				11.4 ± 4.6	
Mean wall area post (mm ²)	6.9 ± 3.4	0.19			4.4 ± 2.1	0.99
Mean wall area follow-up (mm ²)	6.3 ± 3.6				4.4 ± 1.9	
Change in wall area (mm ²)	0.6 ± 1.5				0.0 ± 1.4	

All comparisons post vs follow-up with paired Student's t-test. ns=not significant.

for more than 28 days. All lesions were pre-dilated before stent implantation. At 6 months follow-up a control angiogram with intravascular ultrasound was scheduled. Patients were treated indefinitely with aspirin 100 mg . day⁻¹. A 300 mg loading dose of clopidogrel was given before the procedure followed by 75 mg . day⁻¹ for 8 weeks.

The protocol was approved by the local ethical committee and all patients gave written informed consent.

Quantitative coronary angiography and quantitative intravascular ultrasound

Angiography in multiple projections was performed on pre-procedural, post-procedural and 6 month follow-up angiograms. Off-line quantitative analysis was performed with the Cardiovascular Angiographic Analysis System (CAAS II) using two matched X-ray gantry projections as described elsewhere^[11]. Two analyses were performed, an analysis of only the stented part of the vessel and an analysis of the complete vessel segment including the stent from the nearest proximal to the distal side branch. The latter was done to allow recognition of edge restenosis.

Post stenting and at 6 months follow-up, stented vessel segments were examined with mechanical intravascular ultrasound (CardioVascular Imaging System (CVIS), Sunnyvale CA, U.S.A.) using automated pull-back at 0.5 mm per second. A coronary segment beginning 10 mm distal to and extending 10 mm proximal to the stented segment was examined. A computer based contour detection program was used for automated 3-D reconstruction of the stented segment from up to 200 cross-sectional images. Lumen and stent boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as $V = \sum_{i=1}^n A_i \cdot H_i$, where V=volume, A=total vessel, stent or lumen area (as desired) in a given cross-sectional image, H=thickness of the coronary artery slice, and n=number of slices^[12,13]. Neointimal volume was

calculated as stent volume – luminal volume. Percentage obstruction volume was calculated as neointimal volume/stent volume*100 at 6 months follow-up. For the segments proximal and distal to the stent the vessel area was measured at each cross-section as the area lying within the external elastic lamina. Wall area was then calculated as vessel area–lumen area.

Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated in vitro and in vivo^[12,13]. The quantitative ultrasound analyses were performed by an independent core laboratory (Cardialysis bv, Rotterdam, The Netherlands).

Results

Stents were implanted in 15 patients. Baseline characteristics are summarized on Table 1. One patient died 1 day after successful stent implantation procedure because of intra-cerebral bleeding. She had received abciximab during the procedure and for 12 h thereafter. One patient suffered a vessel occlusion during the procedure due to distal edge dissection. This was successfully treated with additional stenting. No CKMB rise was noted. One additional patient suffered a subacute occlusion of the circumflex artery 2 h after the procedure. He was brought back to the catheterization laboratory and additional stenting of a distal dissection was performed. Maximal CKMB was 42 U.l⁻¹. Subsequent clinical follow-up was uneventful for both patients and at angiographic follow-up no restenosis was found. At 6 months follow-up one patient refused repeat angiography.

At 9 month follow-up, all 14 patients were in CCS angina class I and no further major adverse events had occurred.

Quantitative coronary angiography and quantitative intravascular ultrasound results are summarized on Tables 2–4. No patient had angiographic restenosis (>50% DS at follow-up angiography). Only minimal intimal hyperplasia and no stent malapposition was

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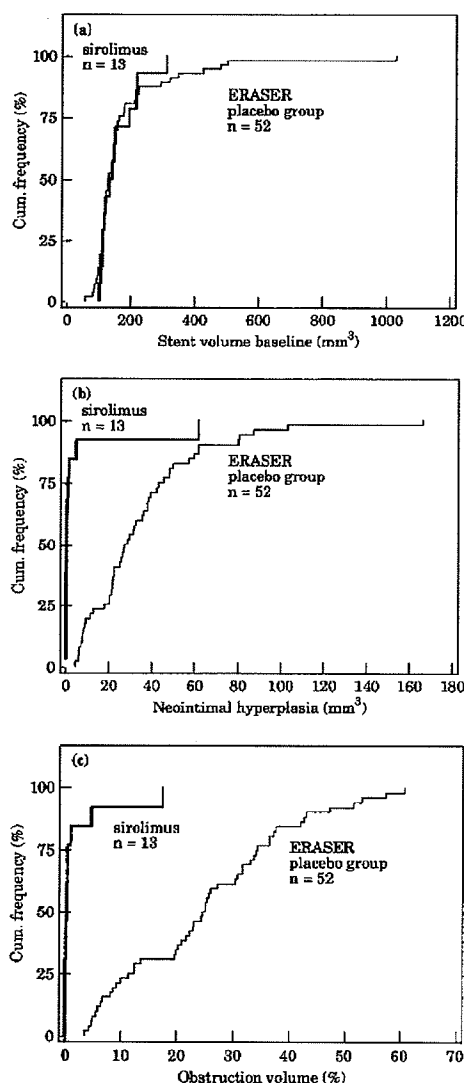


Figure 1 Cumulative distribution curves of stent volume post-implantation (a), in-stent neointimal hyperplasia volume at follow-up intravascular ultrasound (b) and percent obstruction volume at follow-up intravascular ultrasound (c) for the 13 patients treated with sirolimus eluting stents (bold line) and for 52 placebo patients treated with a bare metal Palmaz-Schatz stents in the ERASER study¹⁴ (medium line). Although stent volume post-procedure is similar, the neointimal and percent obstruction volume curves are significantly shifted to the left for the sirolimus group ($P<0.01$, unpaired Student's t-tests).

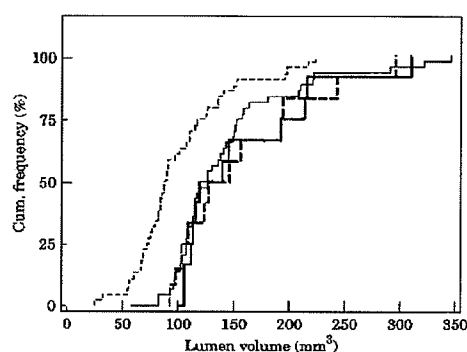


Figure 2 Cumulative distribution curves of in-stent lumen volume immediately post-implantation and at follow-up for the sirolimus eluting stent patients and ERASER placebo group patients with both an intravascular ultrasound measurement immediately post-implantation and at the 6 month follow-up. The sirolimus curves almost completely overlap indicating no change in lumen volume during the follow-up period, while the follow-up lumen volume curve of the ERASER population is significantly shifted to the left ($P<0.001$, paired Student's t-test). Bold curve: sirolimus immediately post-implant. Bold broken curve: sirolimus at follow-up. Medium curve: bare metal stent immediate post-implant. Medium broken curve: bare metal stent at follow-up.

noted on intravascular ultrasound at follow-up angiography (Table 3). No change in lumen area or vessel wall thickening was observed in the vessel segments proximal and distal to the stent, suggesting the absence of an edge-effect after sirolimus eluting stent implantation (Table 4).

Discussion

We found that intimal hyperplasia after sirolimus eluting stent implantation for obstructive coronary artery disease was almost negligible 6 months after the procedure.

To illustrate that vessels treated with a sirolimus eluting stent behave differently from vessels treated with bare metal stents, the cumulative distribution curves of the stent volume post-procedure, in-stent neointimal volume and in-stent percent obstruction volumes of the sirolimus treated arteries have been plotted and compared to the results in vessels treated with 15 mm Palmaz-Schatz bare metal stents from the placebo arm of the ERASER study¹⁴. Although stent volume immediately post-implantation is similar, the neointimal volume curves and percent obstruction volume curves at 6 months are shifted to the left, demonstrating a significant difference in neointima formation between the sirolimus eluting and bare metal stent populations ($P<0.01$, unpaired Student's t-test) (Fig. 1). This is also

illustrated in Fig. 2; in-stent lumen volume does not change during follow-up in the sirolimus eluting stent population ($P=0.99$, paired Student's *t*-test) while the curve for the bare metal stents is significantly shifted to the left at follow-up ($P<0.001$, paired Student's *t*-test). It should be mentioned, however, that the Palmaz-Schatz stent is a first generation stent and possibly associated with a higher restenosis rate than the 3rd generation bare BX VELOCITY stent.

Sousa *et al.*^[10] reported similar findings in their 30 patients. However, in their study follow-up angiography was performed at 4 months. The present study indicates that the positive effects observed extend for at least 6 months.

Another difference between the Rotterdam and Sao Paulo patient groups concerns the size of the vessels treated. The average reference diameter in the Rotterdam patients was approximately 2.75 mm versus approximately 3 mm in the Sao Paulo patients. It is remarkable that in these vessels, that are generally considered as at higher risk^[15], no restenosis was observed.

There were patients with a negative loss in mean luminal diameter at follow-up. After implantation of a balloon expandable stent this would mean malapposition of the stent at follow-up since in these patients the vessel lumen appears to have been enlarged. Malapposition was, however, not seen with intravascular ultrasound at follow-up. This negative loss in mean luminal diameter can best be explained by the long term measurement variability of the CAAS quantitative coronary angiography system. The standard deviation of the long-term difference of mean luminal diameter measurements at two different angiography sessions was earlier found to be 0.36 mm^[16]. Measurements of small negative losses fall within the long-term measurement variability of the quantitative coronary angiography system and therefore do not necessarily mean vessel enlargement.

There is concern in some quarters that locally delivered sirolimus may only delay the restenosis process rather than prevent it, similar to the phenomenon observed after implantation of radioactive coronary stents^[17,18]. Long-term follow-up studies in humans are clearly needed to address this issue. Therefore, the Sao Paulo patient group will undergo follow-up angiography at 12 months and repeat angiography with intravascular ultrasound is planned at 18 months in our patients.

Another concern, based on experience with radioactive coronary stents^[19], is the possibility of intimal hyperplasia occurring at non-exposed or partly exposed areas of the coronary vessel. Therefore we carefully evaluated the vessel segments both proximal and distal to the stented segment and found no evidence of enhanced narrowing or wall thickening in these segments.

Conclusions

Results of the first 45 patients treated with this new eluting stent are very favourable and hold promise for

the future. Whether sirolimus eluting stents will alter the long-term clinical course after percutaneous coronary angiography and for that matter the course of interventional cardiology and bypass surgery, remains to be proven in placebo-controlled randomized trials. Several such trials are currently ongoing in Europe and the United States.

We would like to thank Dr Brian Firth for his critical review of this manuscript and Clemens Disco Msc. for statistical support.

References

- [1] de Feyter PJ, Vos J, Rensing BJ. Anti restenosis trials. *Curr Interv Cardiol Rev* 2000; 2: 326-31.
- [2] Mintz GS, Popma JJ, Pichard AD *et al.* Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996; 94: 35-43.
- [3] Hoffman R, Mintz GS, Dussaillant GR *et al.* Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* 1996; 94: 1247-54.
- [4] Kiesz RS, Buszman P, Martin JL *et al.* Local delivery of enoxaparin to decrease restenosis after stenting: Results of initial multicenter trial. *Circulation* 2001; 103: 26-31.
- [5] Gallo R, Padurean A, Jayaraman T *et al.* Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 1999; 99: 2164-70.
- [6] Burke SE, Lubbers NL, Chen YW *et al.* Neointimal formation after balloon-induced vascular injury in yucatan minipigs is reduced by oral rapamycin. *J Cardiovasc Pharmacol* 1999; 33: 829-35.
- [7] Gregory CR, Huang X, Pratt RE *et al.* Treatment with rapamycin and mycophenolic acid reduces arterial intimal thickening produced by mechanical injury and allows endothelial replacement. *Transplantation* 1999; 59: 655-61.
- [8] Gregory CR, Huie P, Billingham ME, Morris RE. Rapamycin inhibits arterial intimal thickening caused by both alloimmune and mechanical injury. *Transplantation* 1993; 55: 1409-18.
- [9] Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Marks AR. Rapamycin inhibits vascular smooth muscle cell migration. *J Clin Invest* 1996; 98: 2277-83.
- [10] Sousa JE, Costa MA, Abizaid A *et al.* Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: A quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation* 2001; 103: 192-5.
- [11] Serruys PW, Foley DP, de Feyter PJ. *Quantitative coronary angiography in clinical practice*. Dordrecht/Boston/London: Kluwer Academic Publishers, 1994.
- [12] Li W, von Birgelen C, Hartlooper A *et al.* Semi-automated contour detection for volumetric quantification of intracoronary ultrasound. In: *Computers in Cardiology*. Washington: IEEE Computer Society Press, 1994: 277-80.
- [13] Von Birgelen C, Di Mario C, Li W *et al.* Morphometric analysis in three-dimensional intracoronary ultrasound an in vivo and in vitro study performed with a novel system for contour detection of lumen and plaque. *Am Heart J* 1996; 132: 516-27.
- [14] The ERASER Investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). *Circulation* 1999; 100: 799-806.
- [15] Elezi S, Kastrati A, Neumann FJ *et al.* Vessel size and long-term outcome after coronary stent placement. *Circulation* 1998; 98: 1875-80.
- [16] Reiber JHC, Serruys PW, Kooijman CJ *et al.* Assessment of short-, medium- and long-term variations in arterial dimensions from computer assisted quantitation of coronary cineangiograms. *Circulation* 1985; 71: 280-8.

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- [17] Brenner DJ, Miller RC. Long-term efficacy of intracoronary irradiation in inhibiting in-stent restenosis. *Circulation* 2001; 103: 1330-2.
- [18] Kay IP, Wardch AJ, Kozuma K *et al.* Radioactive stents delay but do not prevent in-stent neointimal hyperplasia. *Circulation* 2001; 103: 14-17.
- [19] Albiero R, Adamian M, Kobayashi N *et al.* Short and intermediate term results of ^{32}P radioactive β -emitting stent implantation in patients with coronary artery disease. The Milan dose-response study. *Circulation* 2000; 101: 18-26.

Ser
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92:11
December
1, 1995

CISTI/ICIST NRC/CNRC
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0009-7322
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CORD086624

A2121

Effect of Thromboxane A₂ Blockade on Clinical Outcome and Restenosis After Successful Coronary Angioplasty

Multi-Hospital Eastern Atlantic Restenosis Trial (M-HEART II)

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Background Antithromboxane therapy with aspirin reduces acute procedural complications of coronary angioplasty (PTCA) but has not been shown to prevent restenosis. The effect of chronic aspirin therapy on long-term clinical events after PTCA is unknown, and the utility of more specific antithromboxane agents is uncertain. The goal of this study was to assess the effects of aspirin (a nonselective inhibitor of thromboxane A₂ synthesis) and sulotroban (a selective blocker of the thromboxane A₂ receptor) on late clinical events and restenosis after PTCA.

Methods and Results Patients (n=752) were randomly assigned to aspirin (325 mg daily), sulotroban (300 mg QID), or placebo, started within 6 hours before PTCA and continued for 6 months. The primary outcome was clinical failure at 6 months after successful PTCA, defined as (1) death, (2) myocardial infarction, or (3) restenosis associated with recurrent angina or need for repeat revascularization. Neither active treatment differed significantly from placebo in the rate of angiographic restenosis: 39% (73 of 188) in the aspirin-assigned group, 53%

(100 of 189) in the sulotroban group, and 43% (85 of 196) in the placebo group. In contrast, aspirin therapy significantly improved clinical outcome in comparison to placebo ($P=.045$) and sulotroban ($P=.006$). Clinical failure occurred in 30% (49 of 162) of the aspirin group, 44% (73 of 166) of the sulotroban group, and 41% (71 of 175) of the placebo group. Myocardial infarction was significantly reduced by antithromboxane therapy: 1.2% in the aspirin group, 1.8% in the sulotroban group, and 5.7% in the placebo group ($P=.030$).

Conclusions Thromboxane A₂ blockade protects against late ischemic events after angioplasty even though angiographic restenosis is not significantly reduced. While both aspirin and sulotroban prevent the occurrence of myocardial infarction, overall clinical outcome appears superior for aspirin compared with sulotroban. Therefore, aspirin should be continued for at least 6 months after coronary angioplasty. (*Circulation*. 1995;92:3194-3200.)

Key Words • angioplasty • myocardial infarction • aspirin • platelets • restenosis

Percutaneous transluminal coronary angioplasty (PTCA), used increasingly to ameliorate the clinical consequences of obstructive coronary atherosclerosis, remains hampered by limitations. Of central importance is the complex vascular response to balloon-induced injury that may lead to acute vessel closure and early complications in 2% to 10% of patients¹⁻³ or to late restenosis and recurrent ischemic events in up to 50% of patients.⁴⁻¹⁰ Considerable evidence implicates platelet-thromboxane A₂ interactions in the vascular response to mechanical injury. In experimental studies, angioplasty is followed by rapid deposition of platelets at the site of injury.¹¹⁻¹³ Platelet activation leads to the

release of thromboxane A₂ and serotonin (which potentiate vasoconstriction and further platelet aggregation), thrombin activation, and release of mitogens such as platelet-derived growth factor. In clinical studies, aspirin pretreatment appears to reduce acute coronary thrombosis and myocardial infarction associated with the PTCA procedure.¹⁴⁻¹⁸ On the other hand, aspirin has failed to influence angiographic restenosis in randomized trials.¹⁷⁻¹⁹ However, the effect of aspirin on clinical events during long-term follow-up after successful PTCA has not been assessed. It also remains unknown whether more potent or more selective antithromboxane agents have greater efficacy in preventing restenosis.²⁰ Therefore, we conducted a prospective, multicenter, randomized study to evaluate the role of thromboxane A₂ blockade on late clinical outcome and angiographic restenosis after successful PTCA. Two forms of thromboxane A₂ blockade were evaluated: a nonselective inhibitor of thromboxane A₂ synthesis (aspirin) and a selective antagonist of the thromboxane A₂ receptor (sulotroban).

Received January 24, 1995; revision received May 18, 1995; accepted July 7, 1995.

From the Multi-Hospital Eastern Atlantic Restenosis Trialists (study chairman, Carl J. Pepine, MD). The participating sites and investigators are listed in the "Appendix."

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Methods

This was the second project developed by the Multi-Hospital Eastern Atlantic Restenosis Trialists (M-HEART II). The rationale and protocol have been presented in detail elsewhere.²⁰

Patient Selection

The M-HEART II institutions and investigators and satellite centers participating in the trial are listed in the "Appendix." Patients undergoing planned PTCA of at least one coronary lesion >60% in diameter stenosis were eligible for the study. Patients were excluded if any of the following were present: (1) history of Q-wave myocardial infarction or thrombolytic therapy within 3 days of PTCA, (2) hemorrhagic diathesis, (3) platelet count <100 000/mm³, (4) significant gastrointestinal bleeding, (5) central nervous system disease, (6) allergy to aspirin, (7) blood pressure >180 mm Hg systolic or 120 mm Hg diastolic immediately before initiation of study medication, (8) creatinine clearance <40 mL/min, (9) women of childbearing potential, or (10) left main coronary artery stenosis >30%.

Study Design

M-HEART II used a double-blind, placebo-controlled design with three parallel arms: two antithromboxane therapies and placebo. The primary outcome variable was late clinical failure after an initially successful PTCA. The study protocol was approved by the institutional review board at each center. After giving informed consent, patients were randomly assigned to one of three treatment groups before PTCA: placebo, aspirin (325 mg daily), or sulotroban (800 mg every 6 hours). Treatment was continued for 6 months, at which time follow-up coronary angiography was performed.

Drug Administration

Study drugs were administered in a double-blind fashion with randomization performed off-site by a central facility to ensure that personnel at each institution remained blinded. Study treatment was initiated on the morning of scheduled PTCA at least 1 hour before the planned procedure. Medications were administered in double-dummy fashion with aspirin or comparable placebo administered once daily and sulotroban or comparable placebo administered every 6 hours. After initiation of the study drug, use of any antiplatelet medications or oral anticoagulants were prohibited. Antianginal medications were continued before and after PTCA at the discretion of the clinical investigators.

Angioplasty Procedure and Angiographic Analysis

All patients received aspirin 325 mg on the day before PTCA because of the proven efficacy of aspirin pretreatment in reducing acute procedural ischemic complications.¹⁴⁻¹⁸ PTCA was performed using conventional balloon catheter techniques. During the procedure, intravenous heparin was given as a bolus of 10 000 units followed by a continuous infusion at 1000 U/h. Successful PTCA was defined as a residual diameter stenosis <50% after dilatation.

Coronary artery stenoses were assessed before and after angioplasty in two or more orthogonal angiographic views after the administration of intracoronary nitroglycerin. Field magnification and projection angles were recorded before PTCA, and matching views were obtained for all subsequent angiograms. All cineangiograms were submitted to a core laboratory for analysis. Quantitative measurements of stenosis severity were made using a computer-based analysis as described elsewhere.²¹ For patients to qualify for inclusion in the study, PTCA had to be performed on at least one lesion with a ≥60% diameter stenosis confirmed by the core angiographic facility. Because the results achieved at the core lab were reproducible within ±4% for repeated measurements of percent diameter stenosis, patients found to have a baseline percent stenosis

between 56% and 60% were allowed to continue in the study provided that the stenosis was improved by ≥10% after PTCA. Patients with no stenosis determined by the core laboratory to be ≥56% were discontinued from the study because the intent was to treat only those with significant stenoses. The baseline percent diameter stenosis was determined as the greatest diameter reduction observed in the single "worst" angiographic view. This same angiographic view was used for quantitative analysis of the post-PTCA and 6-month follow-up angiograms. Observers performing the quantitative coronary analysis were blinded to the assigned therapy.

Follow-up

Comprehensive clinical evaluations of patients were scheduled at 2, 6, 12, 18, and 26 weeks. An additional evaluation was repeated at 1 to 2 weeks in the posttreatment phase. Interim history, drug compliance, physical examination, 12-lead ECG, and clinical laboratory testing were performed at each follow-up visit. Pill counts were done to determine the actual number of tablets taken. Patients taking less than 80% of study medication on each of two consecutive visits were considered noncompliant and were withdrawn from the study. All patients prematurely withdrawn from the study, due to noncompliance or adverse side effects, were adjudicated in a blinded fashion by a data monitoring committee. In compliant patients, follow-up coronary angiography was performed at 26±2 weeks, at which time the study medication was discontinued. Early angiography before 24 weeks was performed when clinically indicated. Patients undergoing early restudy, in whom a ≥50% diameter stenosis at the site of dilatation was found, were considered to have a clinically significant restenosis, and study medication was discontinued. In patients undergoing coronary angiography before 24 weeks in whom no restenosis was found, the study drugs were continued and follow-up angiography was repeated at 6 months.

Assessment of Treatment Efficacy

The primary outcome variable was late clinical failure occurring after initially successful PTCA. This was defined as any of the following: (1) cardiovascular death, (2) myocardial infarction, (3) restenosis associated with recurrent angina, or (4) restenosis leading to a recommendation for additional myocardial revascularization procedures. For simplification of reporting, these later two categories are henceforth termed "clinically important restenosis." Myocardial infarctions were documented by elevation in cardiac enzymes accompanied by typical symptoms and ECG changes. Patients with acute ischemic complications associated with the initial PTCA were classified as procedural failures and thus were excluded from the primary outcome analysis of late clinical events. Angiographic restenosis was used as a secondary outcome variable. Restenosis was defined as diameter stenosis ≥50% measured on the follow-up angiogram. Restenosis rates were calculated both by lesion and by patient. All successfully dilated lesions were used in the analysis of the lesion restenosis rate. Patients who underwent multilesion PTCA were considered to have restenosis if any successfully dilated site demonstrated angiographic restenosis.

Sample Size Considerations and Statistical Analysis

To determine the sample size, it was assumed that the rate of late clinical failure would be approximately 30% in the placebo group and that a 50% reduction in the late clinical failure rate would be a clinically relative important change that would justify 6 months of therapy with one of the study agents. A three-armed trial with 500 patients completing the study and eligible for end point analysis was required in order to attain a β error of 0.20 and a two-tailed α error of 0.05 (with correction for multiple comparisons using the Bonferroni method). All clinical and angiographic data were collected on standardized forms and forwarded to the Coordinating Center for entry into

a computerized database. Quantitative data are expressed as mean \pm SD.

Clinical outcome was converted into a binary response: treatment failure or treatment success. Analysis of the response variable was then performed in two ways: first using a parametric method, and second using a nonparametric method. Parametric analysis was performed using the maximum-likelihood log-linear model with effects due to center and treatment. The CATMOD procedure of the Statistical Analysis System (SAS) was used for this analysis. The probability values for the tests of significance correspond to generalized Wald statistic, which is approximately distributed as χ^2 . To justify pooling data across centers, the comparability of results across centers was examined by analyzing the data using a full model with effects due to center, treatment, and center-by-treatment interaction, and by examining the proportions of clinical failures by treatment and center. Since center-by-treatment interaction effect in these analyses was not significant, all probability values for treatment comparisons were obtained from analysis with only the main effects in the model. For nonparametric analysis, the Cochran-Mantel-Haenszel (CMH) χ^2 statistic was used to test for differences in clinical failures between treatment groups controlling for center (investigator). This analysis was performed using PROC FREQ of SAS. The estimates of relative risk and 95% CMH test-based confidence intervals of relative risk for pairwise treatment comparisons were obtained from this analysis.²² A value of $P < .05$ was considered significant for differences in outcomes between treatment groups. Because of the large number of baseline variables compared, a value of $P < .01$ was considered significant for these comparisons.

Results

During a 24-month period, 752 patients were enrolled and received study medication before anticipated PTCA. Of these, 248 were randomized to receive aspirin, 249 to sulotroban, and 255 to placebo. As shown in Table 1, the three groups were not significantly different in terms of baseline clinical and angiographic characteristics.

Fig 1 outlines the patient flow after enrollment and summarizes postrandomization status of subjects for outcomes analysis. A total of 112 patients were excluded because they failed to meet criteria of an initial success-

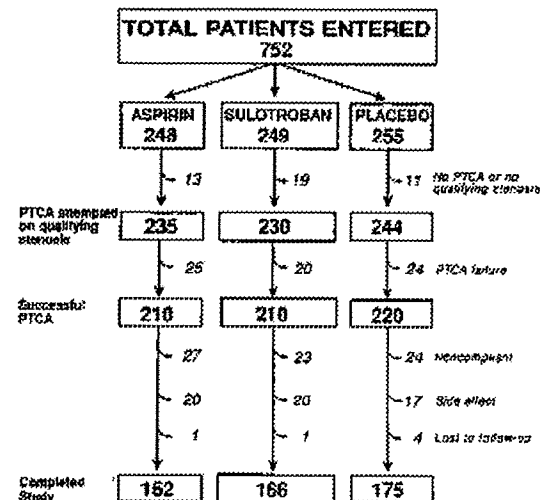


Fig 1. Patient flow diagram. PTCA indicates percutaneous transluminal coronary angioplasty.

ful PTCA, due to one of the following: no PTCA performed or no qualifying stenosis ($n=43$), unsuccessful PTCA procedure ($n=37$), or procedural success by clinical site but post-PTCA stenosis $\geq 50\%$ by core laboratory quantitative analysis ($n=32$). These consequences were not significantly different among the three treatment arms. Procedural success rates were also similar among the three treatment groups. Of the 640 patients who were eligible after the procedure, 57 patients failed to complete follow-up due to side effects and an additional 74 patients were discontinued due to compliance failure as prospectively defined above. Early withdrawals due to drug side effects or noncompliance were not different between the treatment groups. An additional 6 patients were lost to follow-up. Thus, a total of 503 patients were considered eligible for follow-up angiography: 162 in the aspirin group, 166 in the sulotroban group, and 175 in the placebo group. Follow-up angiography was performed in 483 (96%) of these 503 eligible patients.

Angiographic Outcome

The initial procedural success of PTCA was not affected by the study medication, which was started 1 to 6 hours beforehand. Primary angioplasty success without acute procedural complication was achieved in 89.4% of the aspirin group, 91.3% in the sulotroban group, and 90.2% in the placebo group ($P=NS$).

The angiographic restenosis rates by lesion and by patient are summarized in Table 2. Lesion restenosis occurred in 39% (73 of 188) of the aspirin group, 53% (100 of 189) of the sulotroban group, and 43% (85 of 196) of the placebo group. Differences in restenosis rates among the three treatment groups were statistically significant ($P=.020$ by Wald test; $P=.019$ by CMH test). Differences between sulotroban and placebo and between aspirin and placebo were not significant (both $P=NS$). However, the observed difference of 14% between sulotroban and aspirin was significant ($P=.006$). Differences in restenosis rates among the three treat-

TABLE 1. Baseline Characteristics of Treatment Groups

Characteristic	Aspirin, n (%)	Sulotroban, n (%)	Placebo, n (%)
Patients, n	248	248	255
Mean age, y	58 \pm 10	56 \pm 10	58 \pm 10
Men	195 (79%)	211 (85%)	208 (81%)
Clinical findings			
Unstable angina	110 (44%)	130 (56%)	138 (54%)
Prior MI	108 (48%)	119 (48%)	107 (42%)
Prior PTCA	21 (8%)	21 (8%)	23 (9%)
Hypertension	124 (52%)	115 (46%)	128 (51%)
Hyperlipidemia	104 (42%)	106 (43%)	95 (37%)
Diabetes	48 (19%)	46 (19%)	43 (17%)
Smoking (within 1 mo)	60 (28%)	63 (28%)	66 (25%)
Angiographic findings			
Mean diameter stenosis, %	73 \pm 13	80 \pm 13	79 \pm 12
Mean stenosis length, mm	11.6 \pm 3.4	11.4 \pm 3.9	11.7 \pm 3.4
Lesion location			
LAD	61 (39%)	71 (41%)	65 (39%)
LCx	36 (23%)	35 (20%)	38 (21%)
RCA	58 (37%)	60 (35%)	64 (38%)
Graft	2 (1%)	6 (3%)	3 (2%)

MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery.

TABLE 2. Restenosis Outcome

Restenosis	Aspirin	Sulotroban	Placebo
By lesion	73/188 (39%)	100/188 (53%)	85/186 (43%)
By patient	68/159 (44%)	92/161 (57%)	83/164 (51%)
Relative Risk	Odds Ratio	95% Confidence Interval	P
By lesion			
Aspirin vs placebo	0.940	0.569-1.261	NS
Sulotroban vs placebo	1.456	0.958-2.212	NS
Sulotroban vs aspirin	1.795	1.167-2.715	.006
By patient			
Aspirin vs placebo	0.746	0.481-1.156	NS
Sulotroban vs placebo	1.280	0.810-2.022	NS
Sulotroban vs aspirin	1.759	1.119-2.750	.014

ment groups were also statistically significant when analyzed on a per-patient basis ($P=.046$ by Wald test; $P=.050$ by CMH test). Pairwise treatment comparisons indicate that differences in restenosis rates between sulotroban and placebo and between aspirin and placebo were not significant (both $P=NS$). However, the difference between sulotroban and aspirin was significant ($P=.014$).

Primary Outcome

The results of treatment on the 6-month clinical outcome after initially successful PTCA are summarized in Table 3. Odds ratios for the primary outcome of treatment failure are presented in Fig 2. Treatment failure (death, myocardial infarction, or clinically important restenosis) occurred in 30% (40 of 162) of the aspirin group, 44% (73 of 166) of the sulotroban group, and 41% (71 of 175) of the placebo group. Differences in clinical outcome among the three treatment groups were statistically significant ($P=.019$ by Wald test, $P=.021$ by CMH test). There was no significant difference in the treatment failure rate comparing sulotroban with placebo ($P=NS$). On the other hand, aspirin was associated with reduced clinical failure rate compared with either placebo ($P=.046$) or sulotroban ($P=.006$). Importantly, antithromboxane treatment was associated with a significant reduction in acute myocardial infarction during the follow-up period. Myocardial infarction occurred in 1.2% (2 patients) of the aspirin group, 1.8% (3 patients) in the sulotroban group, and 5.7% (10 patients) in the placebo group (aspirin and sulotroban versus placebo, $P=.030$). Fig 3 depicts the time course during which myocardial infarction occurred over the 6-month follow-up period. Among the 17 patients with acute myocardial infarction or death after initially successful angioplasty, the mean interval between the PTCA procedure and the clinical event was 37 ± 31 days. Thus, many of these acute

clinical events occurred relatively late after the initial hospitalization.

Discussion

The results of this trial indicate that thromboxane A₂ blockade improves clinical outcome at 6 months after successful PTCA. Compared with placebo, aspirin was associated with a reduction in late clinical failure, defined as the occurrence of death, myocardial infarction, or clinically important restenosis. The selective thromboxane A₂ receptor antagonist sulotroban also reduced the risk of myocardial infarction during follow-up but was less effective than aspirin in preventing clinical failure. Importantly, a clinical benefit was observed with both antithromboxane treatments even though the rate of restenosis by quantitative coronary angiography was not significantly reduced.

Thromboxane A₂ and Vascular Injury After Angioplasty

The vascular response to balloon injury that leads to restenosis appears to be platelet mediated. Endothelial denudation and exposure of subendothelial collagen to circulating blood results in rapid adhesion of platelets at the site of arterial injury.¹¹⁻¹³ Platelet adhesion and aggregation leads to the release of thromboxane A₂, a potent stimulus for vascular smooth muscle constriction and further platelet deposition. In addition, platelet deposition leads to the secretion of serotonin and plate-

TABLE 3. Clinical Outcomes

Outcome	Aspirin	Sulotroban	Placebo
Treatment success	113 (70%)*†	93 (56%)	104 (59%)
Treatment failure	49 (30%)*†	73 (44%)	71 (41%)
Death	1 (0.6%)	0	1 (0.6%)
Myocardial infarction	2 (1.2%)*	3 (1.8%)*	10 (5.7%)
Clinical restenosis	46 (28%)	70 (42%)	60 (35%)

* $P<.05$ vs placebo.

† $P<.05$ vs sulotroban.

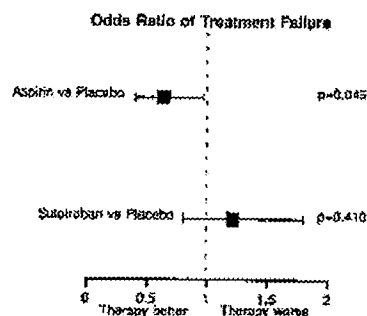


Fig 2. Treatment failure of antithromboxane therapies versus placebo. Results are displayed as odds ratio with 95% confidence intervals. In contrast to sulotroban, which was not significantly different from placebo, aspirin conferred a 37% reduction in treatment failure.

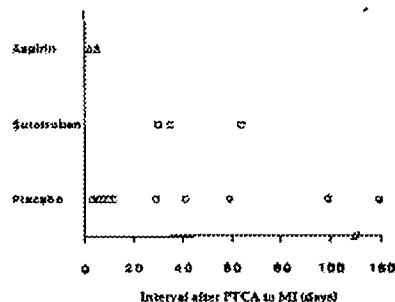


FIG 3. Time plot of myocardial infarctions occurring after initially successful coronary angioplasty. PTCA indicates percutaneous transluminal coronary angioplasty; MI, myocardial infarction.

let-derived growth factors, which promote the neointimal proliferation of smooth muscle cells. Thromboxane A_2 also may promote vascular smooth muscle cell proliferation through a direct mitogenic effect.²³ Thus, by promoting thrombus formation, local vasoconstriction, and cellular proliferation, platelet effects mediated by thromboxane A_2 may participate in the restenosis process that evolves in the weeks to months after coronary angioplasty.

The antiplatelet effect of aspirin is achieved by blockade of thromboxane A_2 synthesis through the nonselective irreversible acetylation of cyclooxygenase.²⁴ While aspirin blocks platelet cyclooxygenase and production of thromboxane A_2 , it also blocks endothelial cyclooxygenase and production of prostacyclin. This latter effect may be deleterious after angioplasty since prostacyclin inhibits platelet adhesion and promotes local vasodilation. Accordingly, use of more selective antithromboxane agents may be more efficacious in the postangioplasty setting. The selective agent used in this study, sulotroban (4,2-benzene-sulfonamidoethyl phenoxycetic acid), is a specific antagonist of the thromboxane A_2 receptor that does not interfere with prostacyclin production or activity.^{25,29}

Prior Studies

In 1984, Thornton and colleagues³⁰ reported results of a nonblinded trial of 248 patients who were randomly assigned after successful PTCA to either aspirin or warfarin. Angiographic restenosis after 6 months of therapy was observed in 27% of patients assigned aspirin and in 36% of patients assigned warfarin ($P=NS$). However, clinical events were not reported. Schwartz et al¹⁷ conducted a double-blind study of the antiplatelet regimen of aspirin (330 mg TID) plus dipyridamole (75 mg TID) compared with placebo beginning 24 hours before PTCA in 376 patients. Restenosis was found in 37% of lesions in both groups. Retrospective analysis of complications occurring within 48 hours of the procedure suggested a lower rate of myocardial infarction in the antiplatelet treated group (1.6%) versus the placebo group (6.9%) ($P=.01$). However, this was not a prospectively defined outcome, and clinical events occurring during later follow-up were not reported. Two other controlled trials that examined the combination of aspirin (650 to 975 mg per day) plus dipyridamole similarly suggested lower rates of acute procedure-related complications but no effect on late restenosis.^{18,19} Limited available data comparing high-dose aspirin versus low-dose aspirin (≤ 325 mg daily) have been inconclusive.³¹

One study of 216 patients, treated initially with aspirin and at 2 weeks assigned to either continued aspirin (100 mg daily) or placebo, suggested a reduction in restenosis with low-dose aspirin.³²

The impact of chronic aspirin therapy after PTCA on long-term clinical outcome after hospital discharge has not been addressed by previous restenosis trials. Late clinical outcome was evaluated as a secondary end point in the Coronary Artery Restenosis Prevention On Repeated Thromboxane-Antagonism (CARPORT) study, which compared the thromboxane A_2 receptor antagonist GR32191B with placebo.³³ No benefit for either angiographic restenosis or clinical events was reported. However, there was no concomitant aspirin-treated group in the CARPORT trial.

Implications of the Present Study

In the current trial, restenosis defined only by quantitative coronary angiography was not prevented by thromboxane A_2 blockade with either low-dose aspirin or a selective receptor antagonist. Although angiographic restenosis was not reduced, thromboxane blockade protected against late clinical events after successful PTCA. The discordance between the clinical and angiographic outcomes may reflect differential effects of thromboxane inhibition. Alternatively, this discordance may reflect the difference in assessment of a time integrated index (clinical events) versus a snapshot of a continuous variable (angiographic patency). The findings of this study has important implications for the design of future restenosis trials. Relying on angiographic end points to the exclusion of patient-related outcomes may result in important biological and clinical effects being overlooked. In contrast to prior angioplasty trials, our primary outcome variable was a censored clinical event rate, not angiographic restenosis. As our study demonstrates, major clinical events including myocardial infarction and death are not limited to the immediate postprocedural days but may occur throughout the following months. Thus, the post-hospital follow-up course of patients after successful PTCA should not be viewed as an inherently benign clinical interim.

The discordance between clinical and angiographic effects suggests that the clinical benefit derived from aspirin is independent of the cellular processes responsible for intimal proliferation. In animal studies, platelet accumulation has been demonstrated at the site of experimentally induced coronary stenoses.³⁴ Furthermore, thromboxane A_2 has been shown by Willerson and colleagues³⁵ to be an important mediator of intermittent coronary obstruction resulting from platelet aggregation and dynamic vasoconstriction. In the canine model of coronary stenosis with endothelial injury, these investigators have demonstrated that cyclical platelet aggregation can be prevented by thromboxane A_2 inhibition. It may be postulated that in patients, the nascent neointimal lesion associated with restenosis may become the nidus for platelet activation modulated by thromboxane A_2 . Thus, while development of the restenotic lesion as the primary event may be relatively independent of thromboxane A_2 , ischemic episodes and acute myocardial infarction may be secondary events triggered by thrombotic and vasoconstrictive processes that are thromboxane mediated. In this light, the vascular injury produced by angioplasty resembles plaque rupture occurring

spontaneously in unstable ischemic syndromes. Three large randomized trials of aspirin in patients with unstable angina have shown a 49% to 72% relative reduction in risk of cardiovascular death or myocardial infarction.³⁵⁻³⁸ In the present study, one aspirin tablet taken daily for 6 months after successful PTCA was associated with a 79% reduction in the risk of myocardial infarction.

Limitations of the Study

All patients received aspirin before PTCA because of its documented benefit in reducing procedural complications including acute myocardial infarction.¹⁴⁻¹⁹ Since the objective of this study was to assess long-term benefits of thromboxane inhibition, our results underscore the importance of continued aspirin therapy after successful angioplasty. On the other hand, the effects of aspirin during the procedure may have mitigated a selective advantage of sulotroban, since prostacyclin synthesis may have been inhibited at the time of vascular injury. Thus, we cannot exclude the possibility that initial administration of aspirin diminished the benefit of thromboxane receptor blockade, since acute procedural events may have influenced later outcomes.

Recently, a unique thromboxane receptor isoform has been identified on endothelial cells.³⁹ This alternatively spliced version of the thromboxane receptor may serve a hemostatic function, inducing a rise in prostacyclin formation upon platelet activation. Accordingly, a thromboxane receptor antagonist that does not distinguish between platelet and endothelial receptors may not be truly selective as an antiplatelet agent. The relative affinity of sulotroban for these thromboxane receptor isoforms is unknown.

Another limitation was the lack of documentation of the degree of receptor blockade achieved with sulotroban and the degree of cyclooxygenase inhibition achieved with aspirin in the study patients. Although patient compliance with the drug protocol was assessed by careful and frequent pill counts, plasma drug levels and ex vivo platelet aggregation studies were not performed. However, we chose doses that had been shown active in previous studies. We also cannot exclude possible contamination of sulotroban or placebo treatment by surreptitious or casual aspirin use. However, the possibility of significant undetected aspirin use in these groups would have been unlikely, since patients were repeatedly instructed to avoid aspirin-containing products at the time of enrollment and at follow-up evaluations. Most importantly, significant differences in clinical outcomes were observed between the groups assigned to aspirin and placebo, indicating a therapeutic benefit of aspirin that would not have been observed if frequent aspirin use in the placebo group had occurred.

Conclusions

Our results indicate that thromboxane A₂ blockade protects against late ischemic events after coronary angioplasty, even though the angiographic restenosis rate is not reduced. While both aspirin and sulotroban reduce the incidence of acute myocardial infarction during follow-up, overall clinical outcome is superior with aspirin. Therefore, aspirin therapy should be maintained in patients for a minimum of 6 months after successful coronary angioplasty.

Appendix

M-HEART II Study Group

M-HEART Study Chairman

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Acknowledgments

The M-HEART II Study was supported in part by a grant from SmithKline Beecham Pharmaceuticals. We thank Laraine Bartlett for her excellent assistance in preparing the manuscript.

References

- Bredlau EC, Koubia GS, Leimgruber PP, Douglas JS, King SB, Gruntzig AR. In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty. *Circulation*. 1985;72:1044-1052.
- Steffenino G, Meier B, Finci L, Yelebit V, von Segesser L, Faidutti B, Rutishauser W. Acute complication of elective coronary angioplasty: a review of 500 consecutive procedures. *Br Heart J*. 1988;59:151-158.
- Holmes DR, Holubkov R, Vliestra RE, Kelsey SF, Reeder GS, Dorros G, Williams DO, Cowley MJ, Faxon DP, Kent KM, Bentivoglio LG, Detre K. Comparison of complications during percutaneous transluminal coronary angioplasty: from 1977 to 1981 and from 1985 to 1986: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *J Am Coll Cardiol*. 1988;12:1149-1155.
- Detre KM, Holmes DR, Holubkov R, Cowley MK, Bourassa MG, Faxon DP, Dorros GR, Bentivoglio LG, Kent KM, Myler RK. Incidence and consequences of periprocedural occlusion. *Circulation*. 1990;82:759-760.
- de Feyter PJ, de Jaegere PT, Murphy BS, Serruys PW. Abrupt coronary artery occlusion during percutaneous transluminal coronary angioplasty. *Am Heart J*. 1992;123:1633-1642.
- McBride W, Lange RA, Hillis LD. Restenosis after successful coronary angioplasty. *N Engl J Med*. 1988;318:1734-1737.
- Holmes DR Jr, Vliestra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Gruntzig AR, Kelsey SF, Detre KM, Van Raden MJ, Mock MB. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol*. 1984;53:77e-81e.
- Leimgruber PP, Robin GS, Hoffman J, Cotsonis GA, Meier B, Douglas JS, King SB, Gruntzig AR. Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation*. 1986;73:710-717.
- Nobuyoshi M, Kimura T, Nosaka H, Mitsu S, Ueno K, Yokoi H, Hamasaki N, Honuchi H, Ohishi. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *J Am Coll Cardiol*. 1988;12:616-623.
- Pepine CJ, Hirschfeld JW, Macdonald RG, Henderson MA, Bass TA, Goldberg S, Savage MP, Vetrovec G, Cowley M, Taussig AS, Whitworth HB, Margolis JR, Hill JA, Bove AA, Jugo R, for the M-HEART Group. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. *Circulation*. 1990;81:1753-1761.
- Steele PM, Chesebro JH, Stanson AW, Holmes DR Jr, Dewanjee MK, Badimon L, Fuster V. Balloon angioplasty: natural history of the pathophysiological response to injury in a pig model. *Circ Res*. 1985;57:105-112.
- Lam JYT, Chesebro JH, Steele PM, Badimon L, Fuster V. Deep arterial injury during experimental angioplasty: relation to a positive indium-111 labeled platelet scintigram, quantitative platelet deposition and mural thrombosis. *J Am Coll Cardiol*. 1986;8:1380-1386.
- Wilentz JR, Sandborn TA, Haudenschild CC, Valeri CR, Ryan TJ, Faxon DP. Platelet accumulation in experimental angioplasty: time course and relation to vascular injury. *Circulation*. 1987;75:636-642.
- Barnathan ES, Schwartz JS, Taylor L, Laskey WK, Cleveland JP, Kussmaul WG, Hirschfeld JW. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. *Circulation*. 1987;76:125-134.
- White CS, Chaitman B, Lassar TA, Marcus ML, Chisholm RJ, Knudson M, Morton B, Roy L, Khaja F, Vandormael M, Reitman M. Antiplatelet agents are effective in reducing the immediate complications of PTCA: results from the ticlopidine multicenter trial. *Circulation*. 1987;76(suppl IV):IV-400. Abstract.
- Kent K, Ewell CJ, Kehoe MH, Laveille P, Krucoff MW. Effect of aspirin on complications during transluminal coronary angioplasty. *J Am Coll Cardiol*. 1988;11:132A. Abstract.
- Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Salvatori VA, Henderson M, Bonar R, David PR. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1988;318:1714-1719.
- White CW, Knudson M, Schmidt D, Chisholm RJ, Vandormael M, Morton B, Roy L, Khaja F, Reitman M. Neither ticlopidine nor aspirin-dipyridamole prevents restenosis post PTCA. *Circulation*. 1987;76(suppl IV):IV-213. Abstract.
- Chesebro JH, Webster MWJ, Reeder GS, Mock MB, Grill DE, Bailey KR, Steichen S, Foster V. Coronary angioplasty: antiplatelet therapy reduces acute complications but not restenosis. *Circulation*. 1989;80(suppl II):II-64. Abstract.
- Savage MP, Goldberg S, Macdonald RG, Bass TA, Margolis JR, Whitworth HB, Taussig AS, Vetrovec G, Cowley M, Bove AA, Cleveland P, Hirschfeld JW, Hill JA, Gilmore P, Pepine CJ. Multi-Hospital Eastern Atlantic Restenosis Trial II: a placebo-controlled trial of thromboxane blockade in the prevention of restenosis following coronary angioplasty. *Am Heart J*. 1991;121:1239-1244.
- Bove AA, Holmes DR, Owen RM, Bresnahan JF, Reeder GS, Smith HC, Vliestra RE. Estimation of the effects of angioplasty on coronary stenosis using quantitative video angiography. *Cathet Cardiovasc Diagn*. 1983;11:5-16.
- Libenfeld DE, Stolley PD. *Foundation of Epidemiology*. New York: Oxford University Press; 1994:316-319.
- Hanasaki K, Nakano T, Arita H. Receptor mediated mitogenic effect of thromboxane A₂ in vascular smooth muscle cells. *Biochem Pharmacol*. 1990;40:2535-2542.
- Oates JA, Fitzgerald GA, Branch RA, Jackson EK, Knapp HR, Roberts LJ. Clinical implications of prostaglandin and thromboxane A₂ formation. *N Engl J Med*. 1986;319:689-767.
- Stegmeier K, Pill J, Müller Beckman B, Schmidt FH, Witte EC, Wolff HP, Fatschke H. The pharmacological profile of the thromboxane A₂ antagonist BM 13.177: a new antiplatelet and antithrombotic drug. *Thromb Res*. 1984;35:379-393.
- Darius H, Lefer AM. Antiaggregatory effects of thromboxane receptor antagonists in vivo. *Thromb Res*. 1983;40:663-675.
- Gresle P, Deckmyn H, Amont J, Lemmens J, Janssens W, Vermeylen J. BM13.177, a selective blocker and platelet and vessel wall thromboxane receptors, is active in man. *Lancet*. 1984;1:991-994.
- Fatschke H, Staiger C, Neugebauer G, Kaufman B, Stein K, Endele R, Stegmeier K. The pharmacokinetic and pharmacodynamic profiles of the thromboxane A₂ receptor blocker BM 13.177. *Clin Pharmacol Ther*. 1986;39:145-150.
- Fiddler GI, Lumley P. Preliminary clinical studies with thromboxane synthetase inhibitors and thromboxane receptor blockers. *Circulation*. 1990;(suppl I):I-69-1-78.
- Thornum MA, Gruntzig AR, Hoffman J, King SB III, Douglas JS. Coumadin and aspirin in prevention of recurrence after transluminal coronary angioplasty: a randomized study. *Circulation*. 1984;4:721-727.
- Califf RM, Fortin DF, Frid DJ, Marlan WR III, Ohman EM, Bergstrom JR, Nelson CL, Tcheng JE, Mark DB, Stack RS. Restenosis after coronary angioplasty: an overview. *J Am Coll Cardiol*. 1991;17:2B-13B.
- Taylor RR, Gibbons FA, Cope GS, Cumpston GN, Mews GC, Luke P. Effects of low-dose aspirin on restenosis after coronary angioplasty. *Am J Cardiol*. 1991;68:874-878.
- Serruys PW, Rutsch W, Heyndrickx GR, Danchin N, Mast EG, Wijns W, Rensing BJ, Vos J, Sobbe J. Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A₂-receptor blockade. *Circulation*. 1991;84:1568-1580.
- Walitsky P, Lefer AM, Frasca P, Sznajdman W. Potentiation of coronary vascular platelet adhesion by atrial pacing in the presence of atrial stenosis in dogs. *J Am Coll Cardiol*. 1984;3:1252-1255.
- Willerson JT, Edt JF, McNatt J, Yao SK, Golino P, Anderson HV, Buja LM. Role of thromboxane and serotonin as mediators in the development of spontaneous alterations in coronary blood flow and neointimal proliferation in canine models with chronic coronary artery stenoses and endothelial injury. *J Am Coll Cardiol*. 1991;17:101B-110B.
- Lewis Jr HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty III JE, Schnaper HW, Le Winter MDA, Linares E, Pouget JM, Shharwal SC, Chester E, Damors H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a veterans administration cooperative study. *N Engl J Med*. 1983;309:396-403.
- Cairns JA, Gent M, Singer J, Fainnie KJ, Froggatt GM, Holder DA, Jablonsky G, Kostmk WJ, Melendez LJ, Myers MC, Sackett DL, Sealey BJ, Tanser PH. Aspirin, sulfinpyrazone, or both in unstable angina. *N Engl J Med*. 1985;313:1369-1375.
- Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, Pelletier E, Juneau M, Stasiak J, deGuise P, Pelletier GB, Rinzler D, Waters DD. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med*. 1988;319:1105-1111.
- Raychowdhury MK, Yukawa M, Collins LJ, McGrath SH, Kent KC, Ware JA. Alternative splicing produces a divergent cytoplasmic tail in the human endothelial thromboxane A₂ receptor. *J Biol Chem*. 1994;269:19256-19261.

EXPEDITED REVIEWS

The Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients With Long De Novo Lesions in Small Native Coronary Arteries (C-SIRIUS)

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OBJECTIVES	We assessed the safety and effectiveness of the sirolimus-eluting stent (SES) in treating single de novo long lesions in small native coronary arteries compared to an identical bare metal stent (BMS).
BACKGROUND	The SES was previously demonstrated to reduce restenosis significantly. However, patients with long lesions in small vessels have not been well studied and may define a group at very high risk.
METHODS	The Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients With Long De Novo Lesions in Small Native Coronary Arteries (C-SIRIUS) was a multicenter, randomized, double-blind trial comparing SES versus identical BMS. The primary end point was in-stent minimal lumen diameter (MLD) at eight months. Secondary end points included angiographic restenosis at 8 months, target lesion revascularization (TLR), and major adverse cardiac events (MACE) at 270 days.
RESULTS	A total of 100 patients were enrolled at eight Canadian sites. The in-stent MLD at eight months was 2.46 ± 0.37 mm in the SES compared with 1.49 ± 0.75 mm in the BMS (a 65% increase, $p < 0.001$). Angiographic restenosis occurred in 1 of 44 SES patients (2.3%, with no in-stent restenosis) and in 23 of 44 BMS patients (52.3%, $p < 0.001$). At 270 days, there were two clinically driven TLRs in the SES (4%) and nine in the BMS (18%, $p = 0.05$). The Kaplan-Meier estimate of freedom from MACE at 270 days was 96.0% for SES patients and 81.7% for BMS patients ($p = 0.029$).
CONCLUSIONS	Patients with long lesions in small vessels are at very high risk of restenosis. In these patients, the SES dramatically reduces the risk of restenosis at eight months, translating into an excellent clinical outcome at nine months. (J Am Coll Cardiol 2004;43:1110-5) © 2004 by the American College of Cardiology Foundation

Stent implantation has become the standard percutaneous coronary intervention (PCI) (1-3). However, in-stent restenosis (ISR) within three to eight months has continued to limit the long-term success of this therapy (4). Neointimal

hyperplasia represent a promising approach to prevent ISR (11).

Preclinical experiments of such an agent, sirolimus (rapamycin), suggested efficacy and safety (12,13). A powerful natural immunosuppressive macrocyclic lactone, it inhibits cytokine-mediated proliferation and migration of lymphocytes and smooth muscle cells (14). Incorporated into a biocompatible non-erodable stent polymer, sirolimus is released into the stented vessel segment over a period of 90 days.

Four clinical trials with the sirolimus-eluting stent (SES) have enrolled patients with de novo lesions in native coronary arteries, with a pattern of increasing lesion complexity (determined by vessel size and lesion length) in successive trials. The "First-in-Man" study (15) restricted treatment to the implantation of a single 18-mm stent in vessels 3.0 to 3.5 mm in diameter, guided by intravascular ultrasound. The subsequent Randomized Study with the Sirolimus-Coated Bx-VELOCITY Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) (16) included vessels 2.5 to 3.5 mm in diameter, but still to be covered with a

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hyperplasia has been identified as the main mechanism of ISR (5,6). Predictors of ISR include a reference vessel diameter smaller than 3.0 mm, lesion lengths above 10 mm, and diabetes mellitus (7-9). Although intracoronary brachytherapy is available to treat established ISR (10), stents eluting pharmaceutical agents capable of suppressing neo-

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Manuscript received November 6, 2003; revised manuscript received January 6, 2004, accepted January 12, 2004.

Abbreviations and Acronyms

BMS	= bare metal stent
ISR	= in-stent restenosis
MACE	= major adverse cardiac events
MLD	= minimal lumen diameter
PCI	= percutaneous coronary intervention
QCA	= quantitative coronary angiography
SES	= sirolimus-eluting stent
TLR	= target lesion revascularization

single stent. The pivotal Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial (17) enrolled patients with longer lesions of 15 to 30 mm, again in 2.5 to 3.5 mm vessels. Finally, in E-SIRIUS (18), patients with a target lesion length of 15 to 32 mm in smaller vessels 2.5 to 3.0 mm in diameter, were randomized to the SES versus a bare metal stent (BMS) of identical architecture.

During the same period, in Canada we conducted a randomized, multicenter trial based on the same protocol as E-SIRIUS, targeting the same patients with long lesions, potentially requiring multiple stents, in small coronary arteries—all conditions that are known to increase the risk of restenosis. Contemporary interventional techniques, including direct stenting, were allowed.

PATIENTS AND METHODS

Patients. This study was a randomized, double-blind trial involving eight Canadian teaching hospitals (Appendix). Patients were at least 18 years old, with documented angina pectoris (Canadian Cardiovascular Society angina class 1 to 4), unstable angina (Braunwald classification B and C, I or II), or silent ischemia. Their PCI target had to be a *single* de novo lesion in a native vessel, between 15 and 32 mm in length, and with a diameter stenosis of 50% to 99%. The vessel diameter was limited to 2.5 to 3.0 mm. All angiographic criteria were based on visual assessment. Major exclusion criteria were the same as E-SIRIUS (18). The study protocol was approved by the ethics committee at each participating center, and all patients gave written informed consent.

Study stents. The control stents used were the bare metal Bx-VELOCITY stent (J&J Cordis, Miami Lakes, Florida), which is a balloon-expandable, tubular 316L stainless-steel stent pre-mounted on a monorail balloon-dilation catheter. The study stents, using the same Bx-VELOCITY platform, had a 5- μ m coating consisting of a blend of 33% sirolimus and 67% of a non-erodable polymer. The drug-polymer matrix contains 140 μ g of sirolimus per cm² of surface area. A drug-free polymer topcoat serves as a control drug release barrier, such that 80% of sirolimus is released within 30 days of implantation and with no residual drug by 90 days. The SES (brand name, Cypher) is visually and radiographically indistinguishable from its uncoated counterpart, allowing for the double-blind design of the trial.

Study procedures. As previously described (18), patients were randomly assigned either to sirolimus or control stents by means of sealed randomization envelopes. Neither the operator nor the patient knew which stent would be implanted.

According to standard care, patients were pre-medicated with 81 to 325 mg of aspirin, begun at least 12 h before the procedure, and clopidogrel, administered as a loading dose of 300 mg before or immediately after the procedure. During the procedure, intravenous boluses of heparin were administered to maintain an activated clotting time in excess of 250 s. The use of glycoprotein IIb/IIIa receptor antagonists was left to the investigator's discretion.

Stent implantation followed current accepted techniques, as described (18). One distinguishing feature of this study, compared with previous trials, was to allow "direct stenting" (without lesion pre-dilation) in centers where this was standard practice. The decision to pre-dilate or not was left to the investigator. Heparin was discontinued immediately after the procedure. Patients were discharged on a regimen of aspirin (81 to 325 mg/day indefinitely) and clopidogrel (75 mg/day) for two months only.

Follow-up. Patients were evaluated clinically at 30, 90, 180, and 270 days. A repeat angiographic study was scheduled after eight months in all patients.

Definitions. At the outset we distinguished between "in-stent" and "in-lesion" angiographic variables, with the former referring to the vessel segment inside the stent and the latter including the 5-mm vessel segments adjacent to the proximal and distal stent edges. Late luminal loss was defined as the difference between the minimal lumen diameter (MLD) at eight months and the MLD post-procedure.

Study end points. The primary end point of this study was in-stent MLD at eight months, determined by quantitative coronary angiography (QCA). Secondary end points included: eight-month angiographic in-lesion MLD; in-stent and in-lesion angiographic restenosis ($\geq 50\%$ diameter stenosis by QCA); major adverse cardiac events (MACE)—a composite end point comprising death, myocardial infarction, emergent coronary artery bypass surgery, and clinically driven repeat target lesion revascularization (TLR)—all at nine months; and TLR at nine months. A clinically driven TLR procedure was defined as one done in response to recurrent angina and/or documented ischemia on noninvasive tests (all recorded prior to repeat angiography), with $>50\%$ diameter stenosis by QCA, or $>70\%$ diameter stenosis by QCA in the absence of symptoms.

Offline QCA at baseline, post-procedure, and after eight months was performed by an independent core laboratory (Brigham and Women's Hospital Angiographic Core Laboratory, Boston, Massachusetts). All clinical end points were adjudicated by an independent clinical events committee.

Data management and statistical methods. At each participating center, patients' data were prospectively recorded on standard case report forms. Complete data monitoring

Table 1. Baseline Characteristics*

	Sirolimus Stent (n = 50)	Control Stent (n = 50)
Age (yrs)	60.3 ± 10.6	60.7 ± 9.1
Male gender (%)	70	68
Risk factors		
Diabetes mellitus (%)	24	24
Hyperlipidemia (%)	84	86
Hypertension (%)	56	48
Current smoking (%)	36	38
History		
Prior myocardial infarction (%)	48	42
Prior PCI (%)	8	8
Prior CABG (%)	6	2
Angina†		
Stable (%)	10	14
Unstable (%)	48	54
Post-myocardial infarction (%)	22	8
Multivessel disease (%)	46	34
Targeted artery (%)		
LAD	32	40
LCX	22	24
RCA	46	36
ACC/AHA lesion class B2-C (%)	64	54
Reference vessel diameter (mm)	2.65 ± 0.30	2.62 ± 0.35
Lesion length (mm)	14.5 ± 6.3	12.6 ± 5.2

*Mean ± SD; †According to the Braunwald classification.

ACC/AHA = American College of Cardiology/American Heart Association;
CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society;
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

was performed by an independent clinical research consulting firm (DT Consultant, Montreal, Canada), which forwarded the completed case report forms to the study coordinating center for data entry and analysis. Treatment allocation was unblinded at Harvard Clinical Research Institute after nine-month clinical follow-up for analysis.

However, individual patient assignment has remained blinded for unbiased clinical follow-up to five years. All data were held at the study coordinating center, but the authors of this report had full access to them.

Based on the hypothesis that in-stent MLD by QCA at eight months would be 1.6 mm for the control stent and 2.4 mm for the SES, with a common standard deviation of 0.7 mm, detecting this difference with an 80% power and a two-sided alpha error of 5%, would require a sample size of <60 patients (30 patients per study arm). Adjusting for an 80% compliance with eight-month angiographic follow-up, the sample size of 100 patients was judged adequate. All analyses were based on the intention-to-treat principle. Continuous variables are presented as mean value ± SD, with differences between groups assessed by the Student unpaired *t* test. Discrete variables are presented as counts and percentages, with differences between groups assessed by the Fisher exact test. The Kaplan-Meier method was used to analyze the occurrence of the composite end point of MACE during the nine-month period of follow-up, with differences between event-free survival curves assessed by log-rank test. Statistical significance was assumed at the 5% level (*p* < 0.05).

RESULTS

Between November 2001 and April 2002, we enrolled 102 patients. Two patients were randomized (one in each group) but subsequently deregistered because no study stent implantation was attempted (one patient underwent coronary artery bypass grafting after failure to cross the lesion with a guidewire and one patient was withdrawn from the study after failed predilation with standard balloons). Thus, 100 patients entered the trial for end point analysis, with 50

Table 2. Quantitative Coronary Angiography

	Sirolimus Stent	Control Stent	Difference [95% CI]	p
Before procedure				
Reference vessel diameter (mm)	2.65 ± 0.30	2.62 ± 0.35	0.03 [-0.10, 0.16]	0.61
MLD (mm)	0.77 ± 0.29	0.82 ± 0.26	-0.05 [-0.16, 0.06]	0.38
Diameter stenosis (%)	70.9 ± 10.6	68.5 ± 10.0	2.4 [-1.6, 6.5]	0.24
After procedure				
MLD in-stent (mm)	2.53 ± 0.30	2.50 ± 0.28	0.03 [-0.09, 0.14]	0.67
MLD in-lesion (mm)*	2.23 ± 0.35	2.17 ± 0.37	0.07 [-0.07, 0.21]	0.35
Diameter stenosis in-stent (%)	6.1 ± 9.1	5.2 ± 10.6	0.9 [-3.0, 4.9]	0.64
Diameter stenosis in-lesion (%)	17.5 ± 7.1	18.5 ± 10.0	-1.0 [-4.4, 1.0]	0.57
At 8-month follow-up				
MLD in-stent (mm)	2.46 ± 0.37	1.49 ± 0.74	0.97 [0.72, 1.22]	<0.001
MLD in-lesion (mm)	2.15 ± 0.35	1.39 ± 0.69	0.77 [0.54, 1.00]	<0.001
Late luminal loss in-stent (mm)	0.12 ± 0.37	1.02 ± 0.69	-0.91 [-1.14, -0.67]	<0.001
Late luminal loss in-lesion (mm)	0.12 ± 0.35	0.79 ± 0.74	-0.67 [-0.91, -0.42]	<0.001
Diameter stenosis in-stent (%)	9.3 ± 10.6	44.2 ± 26.5	-34.8 [-43.4, -26.2]	<0.001
Diameter stenosis in-lesion (%)	20.5 ± 10.3	47.8 ± 24.5	-27.3 [-35.3, -19.4]	<0.001
Angiographic restenosis†				
In-stent	0/44 (0.0%)	20/44 (45.5%)	-45.5% [-60.2%, -30.7%]	<0.001
In-lesion	1/44 (2.3%)	23/44 (52.3%)	-50.0% [-65.4%, -34.6%]	<0.001

Continuous variables are presented as mean (SD). *Includes the 5-mm segments proximal and distal to the stent edges; †diameter stenosis ≥50% at follow-up.

Acute luminal gain = difference between MLD after procedure and MLD before procedure; CI = confidence interval; late luminal loss = difference between MLD at 8 months and MLD after procedure; MLD = minimal lumen diameter.

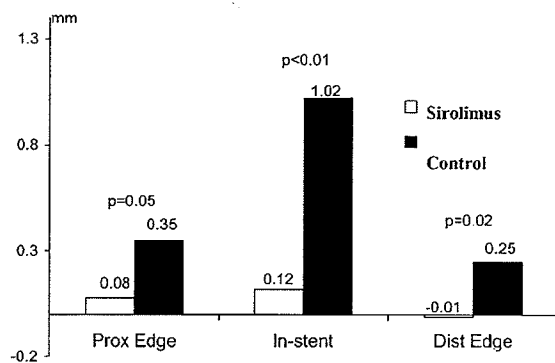


Figure 1. Late luminal loss by quantitative coronary angiography. Proximal edge: the 5-mm proximal to the stent. Distal edge: the 5-mm distal to the stent. Late loss was defined as the difference between the in-stent minimal lumen diameter at follow-up and the post-procedure in-stent minimal lumen diameter.

patients receiving an SES and 50 patients receiving uncoated control BMS. Baseline characteristics of the patients (Table 1) were well matched between groups, with 24% of patients having diabetes mellitus.

Device success, defined as the achievement of <50% residual diameter stenosis with the assigned stent, was 100% in both groups.

The mean lesion length as measured by QCA was 13.6 ± 5.8 mm, in vessels with a mean reference diameter of 2.63 ± 0.33 mm. Glycoprotein IIb/IIIa inhibitors were administered to 53% of patients. The average number of stents implanted was 1.5 ± 0.7 per patient, with two or more stents implanted in 40% of patients. This resulted in a mean total stent length of 23.8 ± 8.4 mm and a stent length to lesion length ratio of 1.8 ± 0.8 . Direct stenting was performed in 31% of cases. Of the stented lesions, 64% were post-dilated (using a shorter balloon in one-half the cases), with a mean maximum pressure of 17.3 ± 3.4 atm and a nominal balloon to artery ratio of 1.0 ± 0.1 .

Immediate post-procedure results were similar for SES and BMS, with a mean in-stent MLD of 2.51 ± 0.29 mm, and residual in-stent and in-lesion stenoses of 5.7% and 17.9%, respectively.

Eight-month angiographic follow-up was available in 88% of patients, with 44 patients in each group. The eight-month in-stent MLD, the primary end point, was significantly greater in the SES group at 2.46 ± 0.37 mm vs. the BMS group at 1.49 ± 0.75 mm (a 65% increase, $p < 0.001$) (Table 2). The corresponding late luminal loss was reduced by 90%, from 1.02 ± 0.69 mm to 0.12 ± 0.37 mm ($p < 0.001$) (Table 2). The eight-month in-lesion MLD was also significantly improved in the SES group compared to the BMS group (Table 2). Consequently, the in-lesion late luminal loss was significantly reduced in the SES patients (Table 2), with an effect demonstrated both at the proximal and distal stent edges (Fig. 1). Angiographic restenosis occurred in 1 of 44 SES patients (2.3%), with no ISR, and in 23 of 44 BMS patients (52.3%, $p < 0.001$). The single SES patient with in-lesion restenosis had a 58% stenosis proximal to the SES stent. The relative reductions in eight-month binary restenosis associated with use of the SES were thus 96% within the lesion and 100% within the stent. No aneurysms were seen.

Major adverse cardiac events at 270 days for all 100 patients are listed in Table 3. There were no deaths and no Q-wave myocardial infarctions. Stent thrombosis occurred in one patient in each group (on day 8 in an SES patient after an initially successful intervention involving three stents in a small right coronary artery, and on day 57 in a BMS patient), requiring TLR in both cases. Eight additional clinically driven TLR procedures occurred in the BMS group and one such procedure in the SES group, for a total TLR rate at nine months of 18% and only 4%, respectively ($p = 0.05$). Only two BMS patients sustained a non-clinically driven TLR following repeat angiography at eight months. Consequently, the Kaplan-Meier estimate of freedom from MACE at 270 days was 96.0% for SES patients and 81.7% for BMS patients ($p = 0.029$) (Fig. 2).

DISCUSSION

Compared with previous trials (15–17), the patients enrolled in this Canadian multicenter controlled trial, along with the E-SIRIUS patients (18), had a higher clinical-risk

Table 3. Major Adverse Cardiac Events Out to 270 Days of Follow-Up

Event*	Sirolimus Stent (n = 50)	Control Stent (n = 50)	Difference [95% CI]	p
Death	0 (0%)	0 (0%)	0% [-, -]	1.00
Myocardial infarction	1 (2.0%)	2 (4.0%)	-2.0% [-8.7, 4.7]	0.58
Q-wave	0 (0%)	0 (0%)	0% [-, -]	1.00
Non-Q-wave†	1 (2.0%)	2 (4.0%)	-2.0% [-8.7, 4.7]	0.58
CABG	1 (2.0%)	0 (0%)	2.0% [-1.9%, 5.9%]	0.25
Clinically driven TLR	2 (4.0%)	9 (18.0%)	-14.0% [-26.0%, -2.0%]	0.05
Total	2 (4.0%)	9 (18.0%)	-14.0% [-26.0%, -2.0%]	0.05

*Non-hierarchical listing; †non-Q-wave myocardial infarction defined as elevation of post-procedure creatine kinase serum levels to more than twice the upper limit of normal, with elevated creatine kinase-MB isoenzyme serum levels, in the absence of new pathological Q-waves.

CABG = coronary artery bypass grafting; CI = confidence interval; TLR = target lesion revascularization by percutaneous coronary intervention.

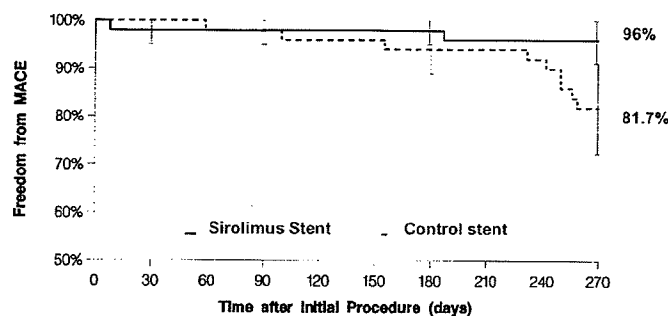


Figure 2. Survival free from major adverse cardiac events (MACE). Absolute risk reduction: 14.3%, $p = 0.029$.

profile for restenosis: long target lesions, small target vessels, multiple stents in 40% of cases, and a mean implanted stent length of 23.8 mm. This is reflected in the progressive increase of the in-lesion restenosis rate of the BMS group: 26.6% in RAVEL (16), 36.3% in SIRIUS (17), 42.3% in E-SIRIUS, and 52.3% in our trial. Despite the higher risk profile of our patients, the eight-month in-stent and in-lesion MLDs were well maintained in the SES patients. Late luminal loss at the proximal and distal edges of the SES was reduced by 77% and 100%, respectively, compared with the BMS, suggesting a true protective effect of the SES at the stent margins. Consequently, the angiographic restenosis rate following SES implantation was only 2.3%, with no ISR. These findings confirm the efficacy of the SES to prevent restenosis, as observed in all previous trials (15–18). Thus, the need for a clinically driven revascularization procedure, prompted by recurrent angina and/or documented ischemia, fell from 18% in BMS patients to 4% in SES patients. This means that for every 1,000 patients undergoing stent implantation for a native coronary artery lesion of the type included in this study, 140 patients may be spared from clinical restenosis and repeat intervention at nine months by initial treatment with SES.

Because the same SES was used in four randomized trials, certain observations regarding the SES patients across the trials may be relevant. The somewhat higher in-lesion restenosis rate observed in SIRIUS (8.9%), compared with RAVEL (0%), E-SIRIUS (5.9%), and C-SIRIUS (2.3%), was associated with more proximal margin restenosis: 5.8% in SIRIUS (especially in patients with the smallest vessels), compared with 0%, 2.1%, and 2.3% in RAVEL, E-SIRIUS, and C-SIRIUS, respectively. This difference could be related to subtle but more frequent or pronounced proximal edge trauma during pre-dilation, stent implantation, or post-deployment dilation, overwhelming the protective effect at the SES proximal margin. The use of direct stenting in E-SIRIUS and C-SIRIUS may also have limited proximal edge trauma and subsequent restenosis in some patients. Taken together with the observation that the total stent length to lesion length ratio of 1.8 in our trial was identical to that in RAVEL and E-SIRIUS suggests that meticulous (and generous)

coverage of all the injured and diseased vessel area appears to be desirable.

CONCLUSIONS

The C-SIRIUS demonstrated that patients with long lesions in small vessels are at very high risk of restenosis. In these patients, the SES dramatically reduced the risk of restenosis, with no ISR at eight months, translating into an excellent clinical outcome at nine months. Ongoing follow-up will evaluate the durability of these clinical benefits over the next four years.

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REFERENCES

1. Fischman DL, Leon MB, Baim DS, et al., for the Stent Restenosis Study Investigators. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496–501.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al., for the Benestent Study Group. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;331:489–95.
3. Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. *JAMA* 2000;284:1828–36.
4. Kastrati A, Schömig A, Dietz R, Neumann FJ, Richardt G. Time course of restenosis during the first year after emergency coronary stenting. *Circulation* 1993;87:1498–505.
5. Gordon PC, Gibson CM, Cohen DJ, Carrozza JP, Kuntz RE, Baim DS. Mechanism of restenosis and redilatation within coronary stents: quantitative angiographic assessment. *J Am Coll Cardiol* 1993;21:1166–74.
6. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol* 1998;31:224–30.
7. Hoffmann R, Mintz GS, Dussallant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* 1996;94:1247–54.
8. Kastrati A, Schömig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 1997;30:1428–36.
9. Bauters C, Hubert E, Prat A, et al. Predictors of restenosis after coronary stent implantation. *J Am Coll Cardiol* 1998;31:1291–8.
10. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001;344:250–6.

11. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: part II. *Circulation* 2003;107:2383-9.
12. Gallo R, Padurean A, Jayaraman T, et al. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 1999;99:2164-70.
13. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation* 2001;104:1188-93.
14. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. *Circulation* 2001;104:852-5.
15. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001;104:2007-11.
16. Morice MC, Serruys PW, Sousa JE, et al., for the RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
17. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
18. Schofer J, Schlüter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomized controlled trial (E-SIRIUS). *Lancet* 2003;362:1093-9.

APPENDIX

Investigators in the Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients With Long De Novo Lesions in Small Native Coronary Arteries (C-SIRIUS): E. A. Cohen (Sunnybrook and Women's College Health Sciences Centre, Toronto), F. Reeves (Centre Hospitalier de l'Université de Montréal, Pavillon Notre-Dame), E. Schampaert (Hôpital du Sacré-Coeur de Montréal), D. Trabulsi (Calgary Heart Centre) L. Title (Queen Elizabeth II Health Science Centre, Halifax), D. Raco (Hamilton General Hospital), S. Plante (Hôpital Laval, Québec), and R. Mildenerger (Victoria Heart Centre). Study coordination: R. E. Kuntz (Harvard Clinical Research Institute [HCRI], Boston, Massachusetts).

For a complete list of the investigators and hospitals participating in C-SIRIUS, please see the March 17, 2004, issue of *JACC* at <http://www.cardiosource.com/jacc.html>.

Articles

Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS)

Joachim Schofer, Michael Schlüter, Anthony H Gershlick, William Wijns, Eulogio García, Erick Schampaert, Günter Breithardt, for the E-SIRIUS Investigators

Summary

Background Sirolimus-eluting stents have been developed to prevent restenosis in the treatment of coronary artery disease. We investigated the risk of restenosis with use of sirolimus-eluting stents compared with bare-metal stents to assess possible differences.

Methods We enrolled 352 patients in whom one coronary artery required treatment, with diameter 2.5–3.0 mm and lesion length 15–32 mm. We randomly assigned patients sirolimus-eluting stents (n=175) or bare-metal stents (control, n=177). At 8 months we assessed differences in minimum lumen diameter and binary restenosis within the lesion (restenosis of $\geq 50\%$ diameter, including 5 mm vessel segments proximal and distal to stented segment). Patients were also followed up for 9 months for major adverse cardiac events. Analysis was by intention to treat.

Findings Stent implantation was successful in 100% of sirolimus-stent patients and 99.4% of controls. The mean diameter of treated coronary arteries was 2.55 mm (SD 0.37) and mean lesion length was 15.0 mm (6.0). Multiple stents were implanted in 170 (48%) patients. At 8 months, minimum lumen diameter was significantly higher with sirolimus-eluting stents than with control stents (2.22 vs 1.33 mm, $p<0.0001$). The rate of binary restenosis was significantly reduced with sirolimus-eluting stents compared with control stents (5.9 vs 42.3%, $p=0.0001$). Significantly fewer patients with sirolimus-eluting stents had major adverse cardiac events at 9 months than did controls (8.0 vs 22.6%, $p=0.0002$), due mainly to a lower need for target-lesion revascularisations (4.0 vs 20.9%, $p<0.0001$).

Interpretation Sirolimus-eluting stents are better than bare-metal stents for treatment of single long atherosclerotic lesions in a coronary vessel smaller than 3 mm in diameter.

Lancet 2003; **362**: 1093–99. Published online Sept 30, 2003.
<http://image.thelancet.com/extras/03art9099web.pdf>
 See *Commentary* page 1088

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Introduction

In the past decade, stent implantation has become the treatment of choice among patients with coronary artery disease.^{1–3} Re-establishment of coronary blood flow with subsequent relief of symptoms can be readily achieved in most patients. However, in-stent restenosis within 3–8 months is the weakness of coronary artery stenting even if heparin-coated stents are used. Dependent on various confounding factors, such as the presence or absence of diabetes mellitus, the size of the targeted coronary artery, the length of the coronary lesion, and the degree of vessel patency achieved by the intervention, restenosis at the site of stent implantation is seen in 15–60% of patients.^{4–8} Neointimal hyperplasia as a response to vessel-wall injury has been identified as the mechanism underlying coronary restenosis after stent implantation.⁹ Intracoronary radiation therapy is available to treat in-stent restenosis,^{10–13} but concepts have evolved to allow the local delivery from the stent of pharmaceutical agents to suppress neointimal hyperplasia.

One such agent is sirolimus, a potent immunosuppressive agent, which inhibits cytokine-mediated and growth-factor-mediated proliferation of lymphocytes and smooth-muscle cells, ultimately by inducing cell-cycle arrest in the late G1 phase.¹⁴ Sirolimus can be incorporated in a stent coating, from which it is released after stent insertion.

In clinical trials of this stent to date,^{15,16} only patients with new lesions in native coronary arteries have been enrolled, and they have followed a staged pattern, with increasing lesion severity determined by vessel size and lesion length. In one pilot study, treatment was restricted to the implantation of one 18 mm stent in vessels 3.0–3.5 mm in size,¹⁵ whereas in the subsequent Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions (RAVEL) trial¹⁶ vessel sizes of 2.5–3.5 mm were allowed, yet lesions still had to be covered with one stent. In the European multicenter, randomized, double-blind study of the SIRIUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (E-SIRIUS) trial, we investigated risk of restenosis among patients who had long atherosclerotic lesions, potentially requiring multiple stents, in small coronary arteries. We compared use of a sirolimus-eluting stent with treatment with a bare-metal stent of identical architecture.

Patients and methods

Patients

Between August, 2001, and February, 2002, we enrolled patients in 35 European clinical centres. Eligible patients had to be aged 18 years or older, with a documented

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diagnosis of angina pectoris (Canadian Cardiovascular Society classification I–IV),¹⁷ unstable angina pectoris (Braunwald classification B and C, I or II),¹⁸ or silent ischaemia. Patients with single-vessel or multivessel coronary disease were eligible, but had to have only one new lesion with an estimated stenosis of more than 50% but less than 100% in a major native coronary artery requiring treatment. The target vessel had to have a diameter of the undiseased segment proximal to the lesion of 2.5–3.0 mm by visual assessment, and target lesion length had to be 15–32 mm also by visual assessment, that could be completely covered by one or two stents. Major exclusion criteria were: evolving myocardial infarction, more than 50% stenosis of the left main coronary artery, which was unprotected by a graft; an ostial, calcified or thrombus-containing lesion; a bifurcation lesion with a diseased major sidebranch (≥ 2.5 mm diameter) that would require stenting; left-ventricular ejection fraction less than 25%; and known allergies to aspirin, clopidogrel, ticlopidine, heparin, stainless steel, contrast agent, or sirolimus. The study protocol was approved by the ethics committee at each participating centre, and all patients gave written informed consent.

Methods

We used bare-metal Bx Velocity stents (control) and coated sirolimus-eluting Bx Velocity stents (both Cordis, Miami Lakes, FL, USA), which are balloon-expandable, tubular, stainless steel stents, premounted and crimped on rapid-exchange balloon-dilation catheters. The sirolimus-eluting stents had a 5 μ m coating consisting of a blend of 33% sirolimus and 67% non-erodible polymer. The drug-polymer matrix contains 140 μ g sirolimus per cm² surface area. A drug-free polymer layer on top of the drug-polymer matrix serves as a diffusion barrier to prolong drug release; around 80% of sirolimus is released within 30 days of implantation. The two types of stent were visually and radiographically indistinguishable. The lengths for both types of stents we used were 8 mm and 18 mm, and they had diameters of 2.5 mm and 3.0 mm.

We randomly assigned patients uncoated or sirolimus-eluting stents by means of sealed randomisation envelopes supplied to each clinical centre from the study coordinating centre (Harvard Clinical Research Institute/Cardiovascular Data Analysis Center, Boston, MA, USA, figure 1). Randomisation was done by clinical centre and treatment group in blocks of ten, ensuring a 1:1 ratio of assigned treatments. Operators and patients were unaware of which stent would be implanted.

According to standard care, patients were premedicated with 100 mg aspirin, started at least 12 h before the procedure, and clopidogrel, administered at 75 mg for at least 3 days before the intervention or as a loading dose of 300 mg before or immediately after the procedure. As an alternative to clopidogrel, 250 mg of ticlopidine could be given twice in the 24 h preceding the intervention. During the procedure, intravenous boluses of heparin were administered to maintain an activated clotting time longer than 250 s. The use of glycoprotein IIb/IIIa receptor antagonists was at the investigator's discretion.

Stent implantation followed standard interventional techniques. We allowed direct stenting (no lesion predilation) in centres in which this was current practice.

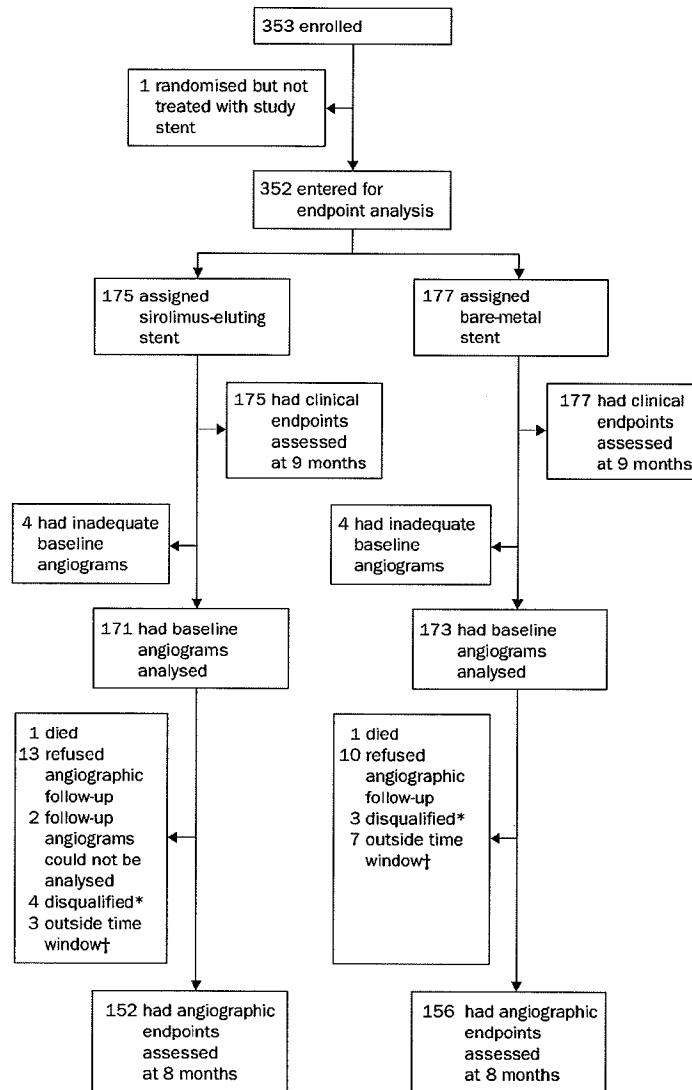


Figure 1: Trial profile

*Follow-up angiography between 2 weeks and 4 months after intervention revealed diameter stenosis 50.0–69.9% but too early to assess primary endpoint and no revascularisation done within 30 days of follow-up date. †Follow-up angiography not done within 9 months of intervention.

The decision to predilate or not was at the investigator's discretion. A maximum of two stents could be implanted to completely cover the lesion. If that could not be achieved, or a dissection occurred, additional stents of the assigned type could be used. Overlapping of stents by 2–4 mm was recommended. Stents were deployed at 10–16 atmospheres of pressure. Postdilation of the stent or stents was also left to the investigator's discretion. The goal of stent deployment was to achieve an angiographic appearance of the expanded stents that was slightly wider than the coronary vessel.

Heparin administration was discontinued immediately after the procedure. The patients were discharged with a regimen of aspirin (100 mg daily indefinitely) and clopidogrel (75 mg daily for 2 months) or ticlopidine (250 mg twice daily for 2 months). We assessed patients clinically at 30 days and 9 months. A repeat angiographic study was scheduled after 8 months.

A priori we distinguished between in-stent and in-lesion angiographic variables, with the former referring exclusively to the vessel segment between the stent edges, and the latter including the 5 mm vessel segments adjacent to the proximal and distal stent edges. Acute luminal gain was defined as the difference between the minimum lumen diameter at baseline and that immediately after placing the stent. Late luminal loss was defined as the difference between the minimum lumen diameter at 8 months and that immediately after the procedure.

Our primary endpoint was the minimum lumen diameter in the stent at 8 months, assessed by quantitative coronary angiography. Secondary endpoints included angiographic binary restenosis (a $\geq 50\%$ diameter stenosis by quantitative coronary angiography) at 8 months; minimum lumen diameter within the lesion (ie, encompassing the 5 mm vessel segments proximal and distal to the stented segment) at 8 months; major

adverse cardiac events—a composite endpoint comprising of death, myocardial infarction, emergency coronary artery bypass surgery, and repeat target-lesion revascularisation—at 9 months; and target-lesion revascularisation at 9 months.

Offline quantitative coronary angiography at baseline, immediately after procedure, and after 8 months was done by an independent core laboratory (Brigham and Women's Hospital Angiographic Core Lab, Boston, MA, USA). All clinical endpoints were adjudicated by an independent clinical events committee.

Statistical analysis

At each participating centre, all patients' data were prospectively recorded on case report forms, which were forwarded to the study coordinating centre for data entry and analysis. Data that were missing, inconsistent, or both were obtained or clarified by direct communication of the study coordinating centre with the respective clinical centre. Data were unmasked when the 9 month clinical follow-up information from all patients had been obtained. All data were held at the study coordinating centre, but the report researchers had full access to them.

We based the sample size on the hypothesis that in-stent minimum lumen diameter by quantitative coronary angiography at 8 months would be 1.95 mm for the uncoated stent and 2.20 mm for the sirolimus-eluting stent, with a common SD of 0.7 mm. Detecting this difference of 0.25 mm, with an 80% power and a two-sided α error of 5%, would require a sample size of 250 patients (125 per study group). With adjustment for higher than 80% adherence to attending 8-month angiographic follow-up, we increased the sample size to 350 patients.

All analyses were based on the intention-to-treat principle. We assessed continuous variables by one-way

	Sirolimus stent (n=175)	Control stent (n=177)	All patients (n=352)*	Difference (95% CI)	p
Demographics					
Mean (SD) age (years)	62.0 (11.4)	62.6 (10.3)	62.3 (10.9)	-0.6 (-2.9 to 1.7)	0.61
Men	123 (70%)	126 (71%)	249 (71%)	-0.9% (-10.4 to 8.6)	0.91
Risk factors					
Diabetes mellitus	33 (19%)	48/176 (27%)	81/351 (23%)	-8.4% (-17.2 to 0.4)	0.08
Hypertension	109/173 (63%)	114 (64%)	223/350 (64%)	-1.4% (-11.5 to 8.7)	0.82
Hyperlipidaemia	132/172 (77%)	124/174 (71%)	256/346 (74%)	5.5% (-3.7 to 14.7)	0.27
Current smoking	63/173 (36%)	53/176 (30%)	116/349 (33%)	6.3% (-3.6 to 16.2)	0.26
History					
Myocardial infarction	71/174 (41%)	76/175 (43%)	147/349 (42%)	-2.6% (-13.0 to 7.7)	0.67
PCI	34 (19%)	39 (22%)	73 (21%)	-2.6% (-11.1 to 5.6)	0.60
CABG	10 (6%)	11 (6%)	21 (6%)	-0.5% (-5.4 to 4.4)	1.0
Comorbidity					
Congestive heart failure	10/174 (6%)	10/174 (6%)	20/348 (6%)	0% (-4.9 to 4.9)	1.0
Symptoms					
Angina CCS class III or IV	73/168 (44%)	70/166 (42%)	143/334 (43%)	1.3% (-9.3 to 11.9)	0.83
Unstable angina	53 (30%)	64 (36%)	117 (33%)	-5.9% (-15.5 to 4.0)	0.26
Number of diseased coronary arteries on angiography					
1	110/173 (64%)	113/175 (65%)	223/348 (64%)	-1.0% (-11.1 to 9.1)	0.91
2	35/173 (20%)	42/175 (24%)	77/348 (22%)	-3.8% (-12.5 to 4.9)	0.44
3	28/173 (16%)	20/175 (11%)	48/348 (14%)	4.8% (-2.5 to 12.0)	0.22
Targeted coronary artery					
LAD	97/171 (57%)	97/173 (56%)	194/344 (56%)	0.7% (-9.8 to 11.1)	0.91
LCX	36/171 (21%)	42/173 (24%)	78/344 (23%)	-3.2% (-12.1 to 5.6)	0.52
RCA	38/171 (22%)	33/173 (19%)	71/344 (21%)	3.1% (-5.4 to 11.7)	0.51
Reference vessel diameter					
Mean (SD) diameter (mm)	2.60 (0.37)	2.51 (0.37)	2.55 (0.37)	0.09 (0.01 to 0.17)	0.025
Lesion length					
Mean (SD) length (mm)	14.9 (5.4)	15.1 (6.5)	15.0 (6.0)	-0.3 (-1.5 to 1.0)	0.76

PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, CCS=Canadian Cardiovascular Society, LAD=left anterior descending coronary artery, LCX=left circumflex coronary artery, RCA=right coronary artery. * Given as n per total.

Table 1: Baseline characteristics

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	Sirolimus stent (n=175)	Control stent (n=177)	Difference (95% CI)	p
Stents implanted				
Single stent	89 (51%)	93 (53%)	-1.7% (-12.0 to 8.7)	0.83
Multiple stents	86 (49%)	84 (47%)	1.7% (-8.7 to 12.0)	0.83
Overlapping stents	60 (34%)	54 (31%)	3.8% (-6.0 to 13.5)	0.49
Mean (SD) total stent length (mm)	23.0 (6.3)	22.2 (6.4)	0.7 (-0.8 to 2.3)	0.32
Mean (SD) total stent length to lesion length ratio	1.7 (0.7)	1.7 (0.7)	0.1 (-0.1 to 0.2)	1.0
Stent technique				
Predilation	130 (74%)	130 (73%)	0.8% (-8.3 to 10.0)	0.90
Direct stenting	45 (26%)	47 (27%)	-0.8% (-10.0 to 8.3)	0.90
Postdilation	59 (34%)	71 (40%)	-6.4% (-16.3 to 3.7)	0.23
Use of glycoprotein IIb/IIIa inhibitors	25 (14%)	31 (18%)	-3.2% (-10.9 to 4.5)	0.47

Table 2: Characteristics of procedures

analysis of variance or unpaired *t* test. We used Fisher's exact test to assess differences in categorical variables between groups. The Kaplan-Meier method was used to analyse the occurrence of the composite endpoint of major adverse cardiac events during the 9-month follow-up period, with differences between curves for survival free from events assessed by the logrank test. We assumed significance at the 5% level ($p < 0.05$).

Role of the funding source

Representatives of the study sponsor assisted in the statistical design of this trial. The study sponsor had no role in the data analysis and data interpretation, in the writing of the report, or in the decision to submit the report for publication.

Results

We enrolled 353 patients. One patient, who had initially been randomised, was excluded because he did not receive the assigned study stent. Thus, 352 patients entered the trial for endpoint analysis, of whom 175 received the sirolimus-eluting stent and 177 the standard uncoated stent (figure 1). Patients' characteristics at

baseline are shown in table 1. There was a higher, but not statistically different, prevalence of patients with diabetes in the control group. The groups were similar for all other characteristics. 116 (33%) patients were current smokers and 148 (42%) had previously sustained a myocardial infarction. Coronary-artery surgery had previously been done in 21 (6%) patients, and 74 (21%) had previously undergone percutaneous intervention for the treatment of coronary lesions other than those targeted in this study.

Less than 50% residual diameter stenosis with the assigned stent—device success—was achieved in 100% of patients given the sirolimus-eluting stents and 99.4% of patients treated with standard stents (this outcome was not assessed in one control because of an inadequate baseline angiogram).

The mean length of the diseased coronary-artery segment of 15.0 mm necessitated implantation of multiple stents in 170 (48%) patients (table 2) because of the lack of long stents. In 114 (67%) of 170 patients who received multiple stents, the implanted stents were overlapping. With a mean total stent length of 22.6 mm, the average ratio of total stent length to lesion length was 1.7. Therefore, on average, lesions in this study were overstented by 70%. Lesions were predilated in 260 (74%) procedures, and direct stenting was chosen in 92 (26%).

The target vessel in controls was on average 0.09 mm smaller than in patients who received sirolimus-eluting stents (table 3). The minimum lumen diameter and the diameter of stenosis at baseline, however, did not differ between treatment groups. Stent placement resulted in identical acute angiographic outcomes, with little difference in acute luminal gain (around 1.5 mm in-stent gain in either group) and no significant difference in in-stent and in-lesion minimum lumen diameter between groups immediately after procedure (table 3, figure 2).

Angiographic data at 8 months were available for 308 (88%) patients, 152 of whom had received sirolimus-eluting stents and 156 control stents (figure 1). In-stent minimum lumen diameter in the sirolimus-stent group

	Sirolimus stent	Control stent	Difference (95% CI)	p
Before procedure				
Reference vessel diameter (mm)	2.60 (0.37)	2.51 (0.37)	0.09 (0.01 to 0.17)	0.025
MLD (mm)	0.90 (0.30)	0.85 (0.31)	0.05 (-0.02 to 0.11)	0.13
Diameter of stenosis (%)	65.1 (10.6)	65.8 (11.2)	-0.7 (-3.0 to 1.6)	0.55
After procedure				
Reference vessel diameter (mm)	2.65 (0.36)	2.56 (0.38)	0.08 (0.01 to 0.16)	0.025
In-stent MLD (mm)	2.43 (0.31)	2.38 (0.33)	0.05 (-0.02 to 0.12)	0.15
In-lesion MLD (mm)*	2.17 (0.39)	2.10 (0.39)	0.07 (-0.01 to 0.15)	0.10
In-stent acute luminal gain (mm)†	1.53 (0.36)	1.52 (0.32)	0.00 (-0.07 to 0.08)	0.79
In-lesion acute luminal gain (mm)†	1.26 (0.41)	1.24 (0.35)	0.02 (-0.06 to 0.10)	0.63
In-stent diameter of stenosis (%)	7.7 (8.5)	6.6 (9.0)	1.1 (-0.7 to 3.0)	0.25
In-lesion diameter of stenosis (%)	18.2 (9.6)	18.0 (9.1)	0.2 (-1.8 to 2.2)	0.84
At 8-month follow-up				
Reference vessel diameter (mm)	2.61 (0.34)	2.48 (0.32)	0.12 (0.05 to 0.20)	0.0006
In-stent MLD (mm)	2.22 (0.48)	1.33 (0.63)	0.89 (0.77 to 1.02)	<0.0001
In-lesion MLD (mm)	1.97 (0.48)	1.29 (0.61)	0.68 (0.55 to 0.80)	<0.0001
In-stent late luminal loss (mm)‡	0.20 (0.38)	1.05 (0.61)	-0.85 (-0.96 to -0.73)	<0.0001
In-lesion late luminal loss (mm)‡	0.19 (0.38)	0.80 (0.57)	-0.62 (-0.73 to -0.51)	<0.0001
In-stent diameter stenosis (%)	14.8 (16.1)	46.9 (24.8)	-32.2 (-36.9 to -27.5)	<0.0001
In-lesion diameter stenosis (%)	24.7 (14.7)	48.3 (23.4)	-23.6 (-28.0 to -19.2)	<0.0001
Binary restenosis§				
In lesion	9/152 (5.9%)	66/156 (42.3%)	-36.4% (-45.0 to -27.8)	<0.0001
In stent	6/152 (3.9%)	65/156 (41.7%)	-37.7% (-46.1 to -29.4)	<0.0001
Proximal stent edge¶	3/146 (2.1%)	13/147 (8.8%)	-6.8% (-11.9 to -1.7)	0.018
Distal stent edge¶	2/152 (1.3%)	16/155 (10.3%)	-9.0% (-14.9 to -3.9)	0.001

MLD=minimum lumen diameter. *Includes the 5 mm segments proximal and distal to the stent edges. †Acute luminal gain=difference between MLD after procedure and MLD before procedure. ‡Late luminal loss=difference between MLD at 8 months and MLD after procedure. Continuous variables presented as mean (SD). §Diameter stenosis >50% at follow-up. ¶Restenosis within the 5 mm segment proximal respectively distal to the stent edge.

Table 3: Quantitative coronary angiography

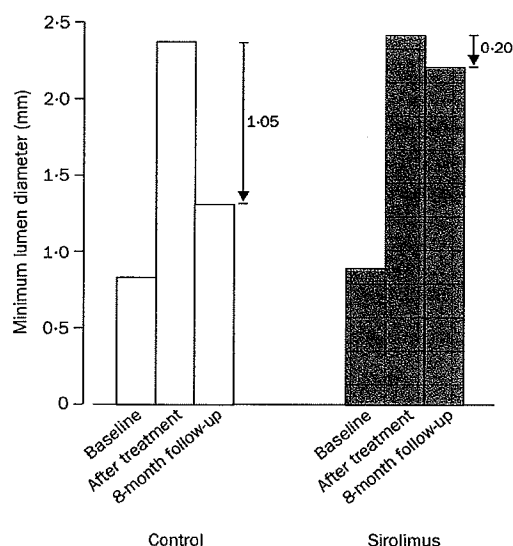


Figure 2: Mean minimum lumen diameter at baseline and within stent after procedure and at 8 months. Arrows represent mean in-stent late luminal loss.

at 8 months was significantly greater than in the control group (2.22 vs 1.33 mm, $p<0.0001$), corresponding with a reduction in late luminal loss of 81% (0.20 vs 1.05 mm, $p<0.0001$; table 3, figure 2). The differences in minimum lumen diameter and late luminal loss were still significant when the 5 mm vessel segments proximal and distal to the stented segment were included (table 3). The significant reduction in late luminal loss translated into significantly reduced proportions of patients with stenosis diameter 50% or more at follow-up in all vessel segments analysed: in-lesion segment (5.9 vs 42.3%, $p<0.0001$); proximal segment (2.1 vs 8.8%; $p=0.018$); within the stent (3.9 vs 41.7%; $p<0.001$); and distal segment (1.3 vs 10.3%; $p=0.001$). The relative reductions in 8-month binary restenosis by use of the sirolimus-eluting stent were, therefore, 86% within the lesion and 91% within the stent.

All 352 patients were followed up for 9 months. Major adverse cardiac events are listed in table 4. Two patients in the sirolimus-stent group died: one man aged 80 years after sustaining a myocardial infarction during the follow-up angiography study, which included an intravascular ultrasound investigation, and a woman

	Sirolimus stent (n=175)	Control stent (n=177)	Difference (95% CI)	p
Event*				
Death	2 (1.1)	1 (0.6)	0.6% (-1.3 to 2.5)	0.62
Myocardial infarction	8 (4.6)	4 (2.3)	2.3% (-1.5 to 6.1)	0.26
Q-wave	2 (1.1)	0 (0)	1.1% (-0.4 to 2.7)	0.25
Non-Q-wave†	6 (3.4)	4 (2.3)	1.2% (-2.3 to 4.6)	0.54
CABG	0 (0)	3 (1.7)	-1.7% (-3.6 to 0.2)	0.25
TLR	7 (4.0)	37 (20.9)	-16.9% (-23.6 to -10.2)	<0.0001
Total	14 (8.0)‡	40 (22.6)	-14.6% (-22.0 to -7.2)	0.0002

CABG=coronary-artery bypass grafting. TLR=target-lesion revascularisation. *Non-hierarchical listing. †Non-Q-wave myocardial infarction defined as rise in post-procedure creatine kinase serum concentrations to >twice upper limit of normal, with raised creatine kinase MB isoenzyme serum concentrations, in absence of new pathological Q waves. ‡Patients might have had >1 event.

Table 4: Major adverse cardiac events to 9 months of follow-up

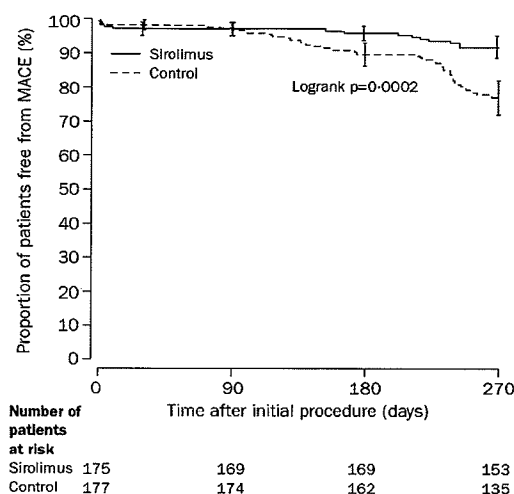


Figure 3: Kaplan-Meier estimates of survival free from major adverse cardiac events. MACE=major adverse cardiac events.

aged 79 years of septicaemia 203 days after the procedure. In the control group, a man aged 54 years died at home 140 days after procedure but the cause of death is unknown. The cumulative rate for death and non-fatal myocardial infarction was 5.1% (nine of 175 patients) in the sirolimus-stent group and 2.8% (five of 177) in the control group (difference 2.3% [95% CI -2.0 to 6.9], $p=0.29$).

Subacute stent thromboses occurred in two (1.1%) patients in the sirolimus-stent group, at 5 and 10 days after procedure, respectively, which resulted in myocardial infarctions (one Q-wave, one non-Q-wave) in both patients. No subacute stent thrombosis occurred in the control group ($p=0.25$ vs sirolimus-stent group). We saw no late stent thrombosis in any study patient.

The overall rate of major cardiac events was significantly better among recipients of sirolimus-eluting stents than among controls (8.0 vs 22.6%, relative reduction 65%, $p=0.0002$; table 4). This difference was primarily driven by a significantly lower rate of repeat revascularisations of the target lesion in patients receiving sirolimus-eluting stents (4.0 vs 20.9%, relative reduction 81%, $p<0.0001$). All target-lesion revascularisations were adjudicated by the clinical events committee as being clinically driven. The Kaplan-Meier estimates of event-free survival for both groups of patients are shown in figure 3. More patients had event-free survival at 9 months with sirolimus-eluting stents than with control stents (91.9 vs 77.2%, $p=0.0002$).

Discussion

Sirolimus-eluting stents improved the rate of event-free survival. Compared with previous studies,^{15,16} the patients enrolled in our study represent a higher clinical risk profile for restenosis: the restenosis rate at 8 months in controls was 42.3%, compared with 26.6% in RAVEL.¹⁶ 42% of our patients had experienced a previous myocardial infarction and 33% were current smokers. Further factors contributing to the increased risk of restenosis in our study patients were the small mean reference vessel diameter, the long average lesion length, and the high rate of multiple stent implantations. By contrast, in-lesion restenosis was only 5.9% among

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patients who received sirolimus-eluting stents, a relative reduction of 86% compared with control stents. Consequently, the need within 9 months for a revascularisation procedure of the target lesion fell from 20.9% among controls to 4.0% among sirolimus-stent patients. Therefore, for every 1000 patients undergoing stent implantation for a native coronary-artery lesion, with sirolimus-eluting stents about 170 will be spared a repeat procedure. The need for repeat target-lesion revascularisation was the major contributor to the overall major adverse event rate in this study, which was significantly reduced with use of sirolimus-eluting stents.

Subacute stent thromboses occurred in two sirolimus-stent patients but in no control. In Sousa and colleagues' study¹⁵ and RAVEL,¹⁶ no stent thrombosis was reported in the sirolimus groups. The difference in the frequency of stent thromboses between our study groups was far from significant and might thus be due to chance. Also, the cumulative rate of deaths and non-fatal myocardial infarctions was higher, but not significantly, among sirolimus-stent patients than among controls.

Sirolimus-eluting stents were efficacious along the entire length of the lesions in our study, which had a more complex patient cohort than Sousa and colleagues' pilot study¹⁵ and RAVEL.¹⁶ Therapeutic efficacy in terms of binary restenosis within the stent and at the proximal and distal stent edges was 91%, 76%, and 87%, respectively. Therefore, lesions and the adjacent vessel segments that might have been injured by predilatation, stent deployment, postdilatation, or a combination of these, were generally well covered with one or multiple appropriately sized stents. Incomplete lesion coverage, arterial trauma outside the stented segment, and a gap between stents, as well as the use of oversized or undersized stents, are possible explanations for treatment failure.¹⁹

The sirolimus-eluting stent maintained its previously demonstrated efficacy in a clinical setting, which we believe resembled a real-world situation. We enrolled patients with a high-risk profile for restenosis, and the interventions incorporated widely practised techniques, such as the implantation of multiple stents and direct stenting. For patients who had faced a likelihood of repeated coronary interventions with use of bare-metal stents, sirolimus-eluting stents might now offer safe and effective treatment. Further studies are, however, required to assess the stent's effectiveness over several years and in other high-risk subsets of patients.

Contributors

All researchers were responsible for the design of this study. M Schlüter wrote the initial draft of the report, which was refined by J Schofer and G Breithardt, before it was sent to the steering committee members, A H Gershlick, W Wijns, E Garcia, and E Schampaeert, for further editing. All researchers discussed and approved the final version.

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Conflict of interest statement

With the exception of E Garcia, researchers have received money for travel to scientific meetings, payment for speaking at meetings, or funding for research from the study sponsor.

Acknowledgment

This study was sponsored by Cordis, a Johnson and Johnson company, the manufacturer of the study stents.

References

- 1 Serruys PW, de Jaegere P, Kiemeneij F, et al, for the Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; **331**: 489-95.
- 2 Fischman DL, Leon MB, Baim DS, et al, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994; **331**: 496-501.
- 3 Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. *JAMA* 2000; **284**: 1828-36.
- 4 Serruys PW, van Hout B, Bonnier H, et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; **352**: 673-81.
- 5 Laham RJ, Carrozza JP, Berger C, Cohen DJ, Kuntz RE, Baim DS. Long-term (4- to 6-year) outcome of Palmaz-Schatz stenting: paucity of late clinical stent-related problems. *J Am Coll Cardiol* 1996; **28**: 820-26.
- 6 Edelman ER, Rogers C. Hoop dreams: stents without restenosis. *Circulation* 1996; **94**: 1199-202.
- 7 Kastrati A, Schömig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 1997; **30**: 1428-36.
- 8 Bauters C, Hubert E, Prat A, et al. Predictors of restenosis after coronary stent implantation. *J Am Coll Cardiol* 1998; **31**: 1291-98.
- 9 Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. *Circulation* 1996; **94**: 1247-54.

- 10 Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997; 336: 1697-703.
- 11 Waksman R, Bhargava B, White L, et al. Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis. *Circulation* 2000; 101: 1895-98.
- 12 Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001; 344: 250-56.
- 13 Waksman R, Raizner AE, Yeung AC, et al. Use of localised intracoronary β radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. *Lancet* 2002; 359: 551-57.
- 14 Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. *Circulation* 2001; 104: 852-55.
- 15 Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001; 104: 2007-11.
- 16 Morice MC, Serruys PW, Sousa JE, et al, for the RAVEL Study Group. Randomized study with the sirolimus-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions: a randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346: 1773-80.
- 17 Campeau L. Grading of angina pectoris. *Circulation* 1976; 54: 522-23.
- 18 Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000; 102: 118-22.
- 19 Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents, part II. *Circulation* 2003; 107: 2383-89.

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Printed in England by Alabaster Pressmore & Sons Ltd., Maidstone, Kent.
Registered as a newspaper at the Post Office, London, E.C.4.

CORD086638

A2142

ASPIRIN AND DIPYRIDAMOLE IN THE PREVENTION OF RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

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Abstract To examine the role of antiplatelet therapy in the prevention of arterial restenosis after percutaneous transluminal coronary angioplasty (PTCA), we conducted a randomized, double-blind, placebo-controlled study in 376 patients. The active treatment consisted of an oral aspirin-dipyridamole combination (330 mg–75 mg) given three times daily, beginning 24 hours before PTCA. Eight hours before PTCA, the oral dipyridamole was replaced with intravenous dipyridamole at a dosage of 10 mg per hour for 24 hours, and oral aspirin was continued. Sixteen hours after PTCA, the initial combination was reinstituted. Treatment was continued in patients with a successfully dilated vessel until follow-up angiography four to seven months after PTCA — or earlier, if symptoms dictated.

Of 249 patients who underwent follow-up angiography,

37.7 percent of patients receiving the active drug had restenosis in at least one segment, as compared with 38.6 percent of patients taking placebo (P not significant). The number of stenotic segments was virtually the same in the two groups. Among the 376 randomized patients, there were 16 periprocedural Q-wave myocardial infarctions — 13 in the placebo group and 3 in the active-drug group (6.9 percent vs. 1.6 percent, $P = 0.0113$).

Although the use of this antiplatelet regimen before and after PTCA did not reduce the six-month rate of restenosis after successful coronary angioplasty, it markedly reduced the incidence of transmural myocardial infarction during or soon after PTCA. Thus, the short-term use of antiplatelet agents in relation to PTCA can be recommended. (*N Engl J Med* 1988; 318:1714-9.)

PERCUTANEOUS transluminal coronary angioplasty (PTCA) is now an established treatment for patients with coronary artery disease. One of the major obstacles to expanding its usefulness is the high incidence of restenosis. Although technological advances have increased the likelihood of success of the procedure itself, they have not altered the restenosis rate, which has remained between 15 and 45 percent.¹⁻⁷

Since the introduction of PTCA in 1977 by Gruentzig, antiplatelet agents have been used shortly before and for up to six months after the procedure in the hope of preventing the recurrence of lesions. This treatment was based on the suspicion, as yet unproved in humans, that platelets initially accumulate on the de-endothelialized intima at the angioplasty site and begin the process that culminates in restenosis.⁸⁻¹⁴ However, no placebo-controlled study demonstrating the efficacy of antiplatelet agents has thus far been published.

In November 1983, we began a prospective multicenter double-blind parallel-group trial to evaluate

the role of an aspirin-dipyridamole combination in reducing the rate of restenosis in patients after successful coronary angioplasty.

METHODS

Between November 1983 and December 1986, 376 patients were enrolled in the study at two participating centers — the Montreal Heart Institute and the Toronto General Hospital. All patients presenting for PTCA at the two centers during this period were considered candidates for the trial. For a patient to be included in the study, at least one lesion under consideration for dilation had to have a diameter of stenosis of 70 percent or more by visual estimation. Patients were excluded for a variety of reasons, as shown in Table 1.

Randomization and Drug Regimen

All aspects of the study protocol were approved by the institutional review board at each medical center. After the patients had given written informed consent, they were randomly assigned in a double-blinded fashion to the placebo or the active-drug group, according to a center-specific, computer-generated schedule. Of the 376 enrollees, 187 were assigned to the active-drug group and 189 to the placebo group.

Patients in the drug group received a combination of aspirin and dipyridamole in a capsule (330 mg–75 mg) 24 and 16 hours before PTCA. Eight hours before PTCA, they were given a 330-mg aspirin tablet and were started on an intravenous infusion of dipyridamole at a dosage of 10 mg per hour. The aspirin dose was administered every 8 hours, and the dipyridamole infusion was continued until 16 hours after PTCA. Combined-drug oral therapy was then reinstituted three times daily with the fixed-dose aspirin-dipyridamole capsules (330 mg–75 mg). In no case was an enteric-coated formulation of aspirin used.

Patients in the placebo group received matching oral and intravenous placebo during the same period. The ampules, tablets, and capsules used for placebo over the entire study period were indistinguishable from the active drug. Both placebo and active drug were packaged and supplied by Boehringer Ingelheim (Canada).

Angioplasty Procedure

Dilazem was given orally in 60-mg doses 12 and 4 hours before the procedure. Heparin (10,000 units) was injected intravenously just before the PTCA and continued at a rate of 200 units per hour to 3 hours. After the groin sheaths were removed at 4 hours, the heparin was resumed at a rate of 500 units per hour for 12 hours.

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CORD086639

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Table 1. Reasons for the Exclusion of 1519 Patients.

REASON	No. OF OCCURRENCES	% OF TOTAL PATIENTS EXCLUDED
Currently taking antiplatelet or anticoagulant drugs	514	33.9
Previous PTCA	327	21.5
No informed consent	131	8.6
History of intolerance to medication or peptic, hepatic, or renal disease	126	8.3
Lives too far from center	126	8.3
Insufficient lead-in time	98	6.5
Dilation of bypass graft	56	3.7
Other angiographic exclusions*	83	5.8
Miscellaneous	53	3.5
	1519	100

*Includes no lesion ≥ 70 percent diameter stenosis by visual reading (1.2 percent), multivesiculated PTCA (1.1 percent), PTCA of total occlusion (0.9 percent), coronary spasm (0.3 percent), and left main coronary artery disease (0.3 percent).

Low-molecular-weight dextran was started at the beginning of the procedure and continued until a total of 500 ml had been administered. Nitroglycerin (200 μ g) was given intravenously just before dilation. These ancillary medications were all part of the standard treatment at both centers when the study began.

The actual dilation was performed with the steerable technique; an attempt was made to attain the best possible angiographic result, with the size of the balloon appropriate to the artery. Electrocardiography was performed before PTCA, immediately afterward, and daily for two days. The creatine kinase level and MB fraction were measured at least once after the procedure in every case.

If a complication necessitating emergency revascularization occurred during or within 48 hours of the PTCA, or if a successful dilation of at least one lesion (reduction of stenosis to 50 percent diameter or less, by visual estimation) was not accomplished, the study medication was discontinued and the patient was treated according to standard medical or surgical procedures. Such patients became ineligible for long-term follow-up to evaluate restenosis, but they were included in the assessment of periprocedural complications.

Follow-up Evaluation

Patients who underwent successful PTCA were discharged from the hospital with one month's supply of medication to be taken with milk or meals. They were asked not to use aspirin or other platelet-active drugs during the study period, and were supplied with acetaminophen for analgesia. They returned at one, three, and five months for a new supply of drugs, a pill count, a clinical examination, and exercise stress testing. Patients were requested to return at four to seven months for follow-up coronary angiography. Any recurrence of symptoms within four months prompted earlier arteriography, but if no definite stenosis was present then, an attempt was made to obtain another arteriogram between the fourth and the seventh months.

Quantitative Coronary Arteriography

All angiograms were analyzed by the computer-assisted system of quantitative coronary angiographic analysis described in detail elsewhere.^{15,16} The analyses were performed in a blinded fashion by experienced technicians under the supervision of radiologists not associated with the angioplasty procedure. Measurements were made in a single projection, showing the most severe stenosis; whenever possible, all three measurements (before and immediately after PTCA, and at final follow-up) were made in the same projection for more accurate comparison. As a rule, the projection that showed the coronary segment in a plane as nearly perpendicular to the axis of the x-ray beam as possible was selected. The variables of interest in this study were the minimum diameter of stenosis (in millimeters) and the maximum percentage of the diameter of stenosis, defined as the ratio of the minimum diameter of stenosis to the reference

diameter (the diameter of the undiseased vessel). We determined that the results attained with this system were reproducible within a margin of 0.12 mm for measurements of diameter and of 3.3 percent for measurements of the percentage of the diameter of stenosis (1 SD for two repeated measurements). These values are similar to those reported byreiber et al.^{15,16}

Definitions and End Points

Restenosis was evaluated both according to the patient and according to the segment. All measurements pertaining to restenosis were determined by quantitative angiographic methods. Only patients with at least one lesion with a diameter of stenosis of 50 percent or more before PTCA that was reduced to less than 50 percent by angioplasty were included in the analysis of restenosis. A patient was defined as having restenosis if at least one such lesion had a diameter of stenosis of 50 percent or more at final angiography. In the evaluation of restenosis according to segment, only segments with a diameter of stenosis of 50 percent or more before PTCA that was reduced to less than 50 percent were considered. A segment was considered restenosed if at final angiography its diameter of stenosis exceeded 50 percent. In order to assess borderline results, the data were reanalyzed with exclusion of all lesions with less than a 10 percent change in diameter of stenosis (3 SD of the estimate of reproducibility).

Periprocedural events were not defined as end points in advance, but were retrospectively classified at the conclusion of the study. Electrocardiograms were interpreted independently by two experienced cardiologists. Myocardial infarction was defined as the appearance of new Q waves, according to the criteria of the Minnesota code.^{17,18} Major periprocedural complications included any one of the following occurring within 48 hours of the index PTCA: death, a Q-wave myocardial infarction, coronary-bypass surgery, or a second PTCA performed on a separate occasion.

Statistical Methods

The minimal sample was estimated at the inception of the study to be 145 patients in each group, on the assumption of a restenosis rate of 30 percent in the placebo group and 15 percent in the drug group (two-sided test with an alpha error of 0.05 and a beta error of 0.20). Differences between treatment groups in the distribution of base-line characteristics and outcome variables were tested by the chi-square test or t-statistic. The differences between the diameter of stenosis immediately after PTCA and that at final angiography were compared between treatment groups by analysis of variance, with the diameter of stenosis before PTCA as covariate. Statistical significance was assessed at the conventional level of 0.05.

Periprocedural complications were analyzed according to the intention-to-treat principle in the 376 patients randomly assigned to the two groups. The primary end point of restenosis required both a successful PTCA procedure according to quantitative criteria and follow-up angiography, and therefore could be evaluated in only 249 patients.

RESULTS

During the course of the study, 1895 patients were screened and 1519 excluded. The reasons for exclusion are summarized in Table 1, the most frequent being the current use of an antiplatelet or an anticoagulant drug that could not be stopped for medical reasons.

Selected demographic, clinical, and angiographic characteristics of the two study groups are shown in Table 2. The only noteworthy base-line difference was a higher percentage of women in the aspirin-dipyridamol group.

Figure 1 shows the patient flow and the reasons that subjects could not be evaluated with respect to angiographic restenosis. Seven patients were randomly as-